Archives of Neurology and Psychiatry

VOLUME 40 NOVEMBER 1938 NUMBER 5

THE TENTORIAL PRESSURE CONE

GEOFFREY JEFFERSON, M.S., F.R.C.S.

MANCHESTER, ENGLAND

In the infancy of tumor diagnosis it seemed sufficient to ascribe the symptoms and signs which were presented in any given case to the destructive or stimulatory effects of the lesion in a purely local sense. As time went by it became apparent that there were apt to be clinical features for which the situation of the tumor would not account. One of the most common and obtrusive of these signs was palsy of the abducens nerve on one or both sides, which was later found to have localizing value only when its presence was supported by some other neighborhood defect, such as paralysis of the facial nerve and perhaps auditory or trigeminal sensory loss. The anatomic observations of Cushing on palsy of the abducens nerve in cases of high pressure, the production by him of preparations showing definite injury to the nerve and the process by which it arises, were the first of a select series which have followed at intervals over ensuing years. Even if his explanations of compression of the nerves by the anterior inferior cerebellar or the internal auditory artery are no longer believed by him, or by others, to be the sole and uniform cause of abducens palsy in cases of high pressure, this observation was the first milestone on the pilgrimage.

Thus prepared, neurologists have come to realize that tumors cause the signs by which one recognizes them in a diversity of ways—interfering with local neural mechanisms by invasion (the glioblastomas) or indentation (the acoustic neuromas); by anemia, local and general (the early and late stages of all benign tumors); by circulatory anomalies of the cerebrospinal fluid (as in disturbances of the third ventricle involving the hypothalamus due to tumors of the posterior fossa or in stretching of the chiasm by the ballooned third ventricle [1]); by shifts; [2]

Based on a paper read at a meeting of the Society of British Neurological Surgeons, London, Jan. 16, 1937.

1. Dott, N. M.: Bitemporal Hemianopia in Relation to Hydrocephalic Distention of the Third Ventricle, Brit. M. J. **2**:296 (Aug. 1) 1936.

2. Cairns, H. W. B.: Observations on the Localization of Intracranial Tumors: The Disclosure of Localizing Signs Following Decompression or Ventriculography, Arch. Surg. **18**:1936 (April, pt. 2) 1929.

by strangulations on dural edges or over taut vessels (affecting most of the cranial nerves, except the first and twelfth, and the crus cerebri),[3] and, last, by foraminal herniations.

Although the most important localizing signs produced by a tumor are those of local destruction or local inhibition or stimulation, one finds, in addition to this truly focal evidence, truly local neuronal disorder, the clinical picture frequently overlaid by other evidences, which are generally of later development. Indeed, cases occur, though uncommonly, in which the only clear evidences of the tumor are those which are the by-products of its hypertensive effects (e. g., papilledema and abducens palsy). Another point, and one which will be brought out later in this communication, is that focal signs which are not discrepant with the known location of the lesion and appear at first glance to be in keeping with that locus may be reenforced and subtly altered by an additional mechanism which one may not have fully taken into account. The picture can, therefore, become one of great complexity, of interwoven consecutive and nonconsecutive signs. Perhaps even now, one rarely assigns correctly every observed fact to its true origin. Since herniation into the incisura tentorii may produce disconcerting and ambiguous effects, it is worthy of fuller discussion than has been allotted to it, though it is not an entirely new subject.

By foraminal herniation in its general sense is commonly meant the best known form, tonsillar (cerebellar) herniation into the foramen magnum. It is known that in cases of high intracranial pressure of long standing other local herniations may complicate the clinical picture, notably those into the foramens in the floor of the middle fossa, producing paradoxic trigeminal pains and even anesthesias (e. g., in cases of occipital and other meningiomas and even in some cases of benign gliomas), and those into the sella.[4] This holds true not only for tumors of the posterior fossa but also for those of the hemispheres producing destruction as a distance effect, a fact which has been in the past a fertile source of error, and is today to the uninitiated. Of all forms of herniation, the best accredited is that into the foramen magnum, tonsillar herniation, the dangers of which Cushing pointed out many years ago, at the same time demonstrating a means of operative treatment. As in earlier days tonsillar herniation (as I prefer strictly to call it, so as to keep it distinguished from other varieties) was known to be associated chiefly with cerebellar tumors, lumbar puncture came

3. (*a*) Cushing, H.: Strangulation of the Nervi Abducentes by Lateral Branches of the Basilar Artery in Cases of Brain Tumour, Brain **33**:204, 1910. (*b*) Kernohan, J. W., and Woltman, H. W.: Incisura of the Crus Due to Contralateral Brain Tumor, Arch. Neurol. & Psychiat. **21**:274 (Feb.) 1929.

4. Cushing, H.: Anosmia and Sellar Distention as Misleading Signs in the Localization of a Cerebral Tumour, J. Nerv. & Ment. Dis. **44**:415, 1916.

to be regarded as a particularly dangerous procedure in cases of lesions of the posterior fossa, and cisternal puncture, when it came into use, as a step not even to be thought of. Yet at times cases were encountered in which there was present the classic sign of impending death from pure medullary compression (cessation of respiration with the heart continuing to beat strongly), while at operation or necropsy the lesion proved to be supratentorial. This paradox has been recognized by clinical neurologists, some of whom will not permit a lumbar puncture to be done in a case of high pressure, whatever the suspected site of the tumor. That there is considerable justification for such an attitude the cases which illustrate this paper will show. It has been assumed that in cases of supratentorial lesions associated with high pressure in which death followed lumbar puncture there must be tonsillar herniation. However, it has not been explained, except in vague terms, how the pressure is transmitted from the hemispheral chambers to the posterior fossa. Clearly, it must be through the tentorium, and if that is so, the presence of a pressure cone at this level must immediately be admitted, unless the whole tentorium can be depressed, squeezing the contents of the posterior fossa (an alternative that has not been proved). A pressure cone at the higher level does exist, and both types can occur together, as will be illustrated in this paper (case 4).

HISTORICAL REVIEW

In 1920 Meyer [5] described and illustrated for the first time herniation into the hiatus or incisura tentorii (space of Bichat) and pointed out that the uncus is the portion of the brain which, from its position, is most liable to this happening. He illustrated the hernia with a series of photographs and a brief note on the site of the tumor in each case (the temporal lobe, postcentral and paracentral gyrus, midbrain, etc.). Two cases were particularly important, as the posterior cerebral artery had been strangulated by the edge of the tentorium, with what Meyer referred to as "collapse of the corresponding part of the occipitotemporal cortex." This was an important paper, but the letterpress which accompanied the photographs was, unfortunately, meager. Two points were evidently in Meyer's mind and were mentioned in the text (but scarcely more): (1) the danger of lumbar puncture in the presence of this complication and (2) the possibility of hemianopia as a false localizing sign, from obliteration of the posterior cerebral artery.

Kernohan and Woltman,[3b] in 1929, called attention to the equivocal signs (ipsilateral paralysis) which can be induced by pressure of the free edge of the tentorium on the crus. They proved the truly pathologic

5. Meyer, A.: Herniation of the Brain, Arch. Neurol. & Psychiat. **4**:387 (Oct.) 1920.

basis of the condition by histologic observations. In 1927, Groeneveld and Schaltenbrand [6] reported a suggestive case of the same order. In the main, the pathogenesis of what has come to be called "the Kernohan-Woltman crescent" is similar to that of the hernia now under discussion, and it is significant that in 1 of the cases reported by Kernohan and Woltman a deep groove on the crus was present on one side and herniation of the uncus on the other. Protrusion of the temporal lobe downward through the tentorial hiatus must tend to thrust the opposite crus against the sharp dural edge, unless it has already been insulated by forced prolapse of the temporal lobe on that side as well, as may occur.

In 1932 Greenfield [7] showed 2 specimens in which the area striata had been deprived of its blood supply by the same mechanism as that discovered by Meyer. One was a massive meningioma in the left parietal area; the other, a colloid ball tumor (paraphysial cyst) of the third ventricle.

In 1934 Spatz and Stroescu [8] published an important paper on the intracranial cisterns and their alterations in cases of high pressure. They illustrated various herniations and pressure markings on the brain. In their discussion on obliteration of the cisterna ambiens, they reproduced excellent photographs of hemispheral prolapse through the incisura tentorii. The cases from which their examples were drawn were those of tumors and abscesses and 1 of bilateral subdural hematoma. In a case of extreme severity a ring of cerebral cortex had been squeezed down through the hiatus, all the way around. In general, in both the cases reported by Meyer and those by Spatz and Stroescu, the area which had most readily prolapsed downward under the influence of high pressure was the uncus. In 1936 van Gehuchten,[9] at the Societé de Neurologie de Paris, insisted on the important role played by the temporal pressure cone in the pathogenesis of this accident. In a more recent paper, Vincent, David and Thiébaut [10] returned to the

6. Groeneveld, A., and Schaltenbrand, G.: Ein Fall von Duraendotheliom über der Grosshirnhemisphäre mit einer bemerkenswerten Komplikation, Deutsche Ztschr. f. Nervenh. **97**:32, 1927.

7. Greenfield, J. G.: Private communication at a meeting of the Society of British Neurological Surgeons, 1932.

8. Spatz, H., and Stroescu, G. J.: Zur Anatomie und Pathologie der äusseren Liquorräume des Gehirns, Nervenarzt **7**:481, 1934.

9. van Gehuchten, M. P.: Le mécanisme de la mort dans certains cas de tumeurs cérébrales, Rev. neurol. **65**:702 (March) 1936.

10. Vincent, C.; David, M., and Thiébaut, F.: Le cône de pression temporal dans les tumeurs des hémisphères cérébraux: Sa symptomatologie, sa gravité, les traitements qu'il convient de lui opposer, Rev. neurol. **65**:536 (March) 1936.

subject first discussed by them in 1930 and spoke more specifically of its clinical manifestations. They noted, as the outstanding signs, acute headache radiating to the occiput, rigidity of the neck, ptosis, somnolence and irregular respiration; "coffee-ground" vomit, pulmonary edema and hyperthermia may also appear as the result of mesencephalic disturbance.

Since the present paper was read, van Gehuchten [11] has described in full the 6 cases which were the basis of his former brief communication. They illustrate the effect of the temporal pressure cone as a cause of death, whether after lumbar puncture or decompression or with no intervention at all. Van Gehuchten drew attention to the hemorrhages of the midbrain and pons which sometimes accompany the pressure cone. He attributed this bleeding to diapedesis from terminal vasomotor paralysis. The pathogenesis of these hemorrhages has been recently discussed by Moore and Stern [12] in an important paper devoted to two subjects in particular: (*a*) infarction in the occipital lobe caused by the pressure cone in cases of neoplasm and (*b*) the hemorrhages of the pons and midbrain seen often in cases of fatal tumor of the brain. Under the first heading they described the examples observed by Greenfield several years ago and already alluded to page 860. Moore and Stern expressed the belief that the lesions of the brain stem are due to a sudden rise in intracranial pressure, a rise which may easily escape clinical detection when the patient is already very ill from the advancing effects of a space-occupying lesion. These hemorrhages are always fatal. They are not, however, invariably present in patients who die of an intracranial tumor. They did not occur in any of the cases which form the basis of the present paper, though they were seen in the first 2 cases observed afterward. They explain, however, the mechanism of fatality in a proportion, as yet unknown, of cases of hemispheral tumors. The pressure cone was further adduced by Smyth and Henderson [13] to account for the difference in the ventricular and the lumbar cerebrospinal fluid pressure readings observed in 8 of 33 patients; 6 of these 8 patients died within twenty-four hours of the estimations, a fact which proves that coincident ventricular puncture is not sufficient to avert catastrophe. Lastly, Le Beau,[14] in his important work on cerebral edema in the clinics of Guillain and Vincent, illustrated fully the tentorial pressure cone and included another type of herniation—that of the cerebellar roof upward through the tentorial hiatus, a state occurring in cases of cerebellar edema.

---

11. van Gehuchten, P.: Le mécanisme de la mort dans certains cas de tumeur cérébrale, Encéphale **32**:113, 1937.

12. Moore, M., and Stern, K.: Vascular Lesions in the Brain-Stem and Occipital Lobe Occurring in Association with Brain Tumours, Brain **61**:70, 1938.

13. Smyth, G., and Henderson, W. R.: Observations on the Cerebro-Spinal Fluid Pressure on Simultaneous Ventricular and Lumbar Punctures, J. Neurol. & Psychiat. **1**:226, 1938.

14. LeBeau, J.: L'edème du cerveau, Recht, Paris, 1938.

In referring to the clinical picture of the temporal cone, he laid stress particularly on rigidity of the neck as a constant occurrence. These recent papers demonstrate once more the interest aroused by the discovery of a gross mechanical phenomenon with profound physiologic significance.

REGIONAL ANATOMIC RELATIONS

As the midbrain passes through the hiatus tentorii it is normally insulated from contact with the free edge by the presence of a buffer of cerebrospinal fluid, the cisterna ambiens. At the sides and behind, the sharp edge of the tentorium fits snugly against this cistern, but in front the gap is wider and more shelving, where the caudal extremity of the cisterna interpeduncularis becomes confluent with the cisterna

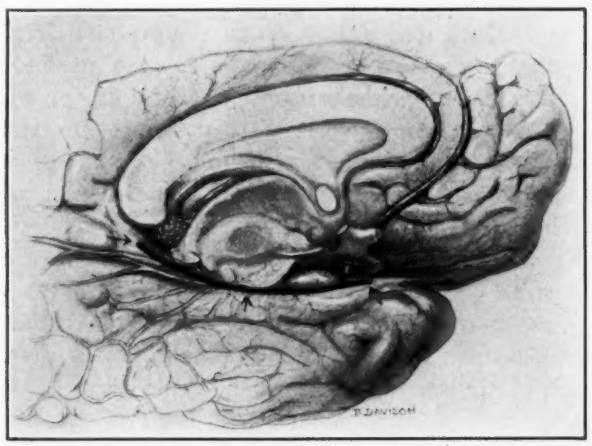


Fig. 1.—Drawing from a normal specimen prepared to demonstrate the line of tentorial contact. Note also the posterior cerebral artery.

pontis. In the formaldehyde-hardened body of the dissecting room, and even in unfixed specimens, it is common to see a shallow groove on the inner surface of the temporal lobe anteriorly, actually on the uncus, where it has come into contact with the most anterior part of the sharp edge of the tentorium, after the deflation of the basal cisterns that occurs post mortem. Ordinarily, this sulcus is not more than 1.5 cm. long and is very shallow, the cortex medial and lateral to it curving away smoothly. In the normal state, therefore, the incisura tentorii is occupied by the caudal end of the midbrain, and what small space there is around the brain stem allows for buffering with cerebrospinal fluid. There is no room for interposition of any extraneous tissues, except anteriorly. Sloping obliquely backward on either side and partly encircling the midbrain lie the posterior cerebral arteries (fig. 1), and it is a matter for surprise that they do not more often suffer from their

close relationship to the sharp edge of the tentorium. No other intracranial vessel is vulnerable in this manner in anything approaching the same degree. When the brain mass is increased by tumor, abscess or edema, or perhaps by hemorrhage, it obtains room by getting rid of cerebrospinal fluid and of blood and will herniate if it can. The drift, like that of the cerebellum toward the spinal canal through the foramen magnum, must be toward an area of low pressure—in the case now under consideration, toward the posterior fossa through the hiatus tentorii. The black line in figure 1 illustrates the position of the free edge of the tentorium relative to the normal brain in situ. Anteriorly, it cuts the uncus, as already mentioned; behind that and for the greater part of its course, it is related to the choroid fissure, while behind it runs only a short distance below the splenium callosi. Considerable, and no doubt long-standing, pressure is necessary to crowd any part of the neighboring structures other than the uncus into the incisura; yet that can take place, as Spatz and Stroescu showed. No perfect illustration of the tentorium seems to exist—none that gives a correct impression of its anteroposteriorly convex upper surface, its lateral decline and the manner of the abrupt falling away of the almost vertically directed anterior 2 cm. or so of its surface, as it changes its architecture to sweep forward onto the sides of the cavernous sinus. The temporal lobes lie on the tentorium, which slopes away laterally as a gently inclined plane, so that pressure from above will tend to make them slide away from the midline. However, if one lobe is enlarged it cannot escape overhanging the free edge. For this reason, a tumor of the temporal lobe will be the surest way of bringing it more firmly into contact with the midbrain and squeezing its inner border over the sharp edge of the falx, into a situation in which it can herniate downward into the posterior fossa. The free edge of the tentorium now cuts deeply into it, and this impression will remain long after the brain has been removed, even if it has not been hardened in situ. There is no doubt that if the tentorium were horizontal herniation would be much more common than it is. Its tentlike form causes it to protect the midbrain. In figure 2 are shown drawings from specimens illustrating unilateral and bilateral herniations. It will be observed that they have been seen in association not only with lesions of the temporal lobe but with distant tumors, even with those of the cerebellum. In 1 case (fig. 2*D*), that of a hemangiomatous cerebellar cyst, there was a double pressure cone, a tonsillar enlargement of the cerebellar mass and a tentorial cone from the resulting hydrocephalus, while in figure 6 is shown a similar double cone produced by a meningioma of the middle fossa. Cerebral abscesses seem to be particularly prone to cause incisural herniation, for two reasons: (1) the edema that accompanies them, and (2) their frequency in the temporal lobe.

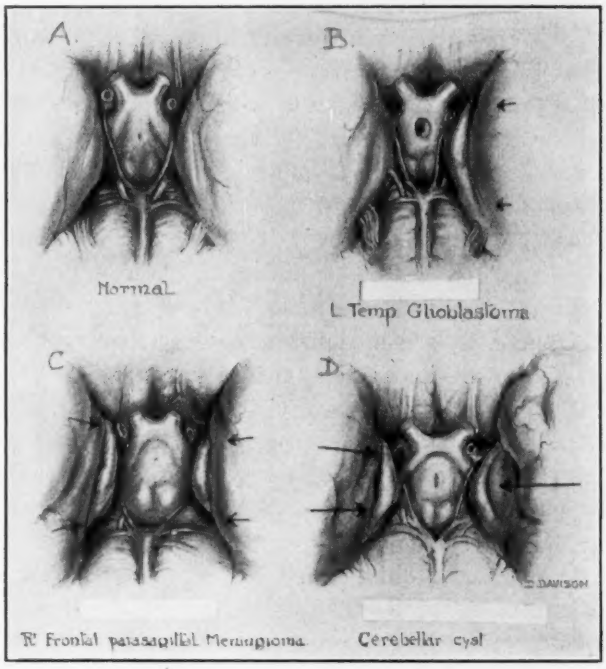


Fig. 2.—*A*, normal uncus with a faint tentorial impression; *B*, *C* and *D*, herniations of the uncus into the hiatus tentorii, caused by tumors in various situations.

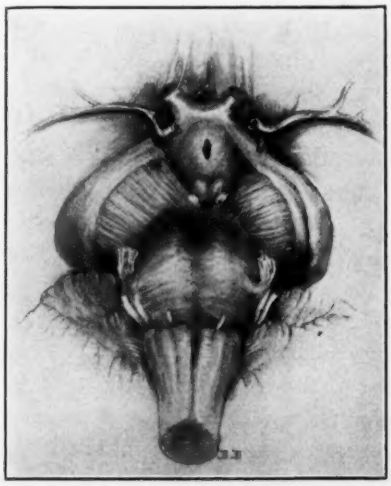


Fig. 3.—The midbrain, in a case of glioma of the right temporal lobe, stripped to show the flattened crus (and optic tract).

The crowding of the temporal lobe into the incisura must have an effect on the crus. In figure 3 is shown the flattened appearance of the crus on one side as compared with its normal fellow in a case of temporal tumor, after the temporal lobe has been stripped away. It will be seen how easily the optic tract may, at the same time, be compressed by the enlarged lobe and be, as Traquair [15] insisted, an important cause of hemianopia in space-occupying lesions of the temporal lobe. The visual fields in many cases of lesions of the temporal lobe are explicable only on the basis of this assumption, and my own experience supports Traquair's view. It must be added that in some cases of this type the visual defect is due, as Cushing demonstrated, to involvement of the temporal loop. This, however, is by the way, for there is no suggestion that the optic tract is compressed by the tentorial pressure cone, for it lies at a higher level.

The possibility that the whole tentorium may sometimes be slightly depressed in cases of tumor of the hemisphere has been mentioned. Although this possibility cannot be completely dismissed, it is difficult to raise it to the level of proof by demonstration. Evidence of the reverse process, elevation of the tentorium by obliteration of the posterior horn of the lateral ventricle by a cerebellar tumor, has been advanced by a few investigators. As careful an observer as McConnell [16] declared that he had seen it, and Foerster recently described a case at a meeting. However, the posterior horns are often absent, whereas if the evidential fact is hemianopia, strangulation of the posterior cerebral artery on the tentorial edge is a more probable explanation.

EFFECTS OF HERNIATION OF THE UNCUS INTO THE INCISURA TENTORII

The cases which follow illustrate the effects produced by the tentorial pressure cone, at the higher level. It will be seen that lumbar puncture is dangerous in persons with symptoms of high pressure, even if signs of high pressure are absent (case 2). The fact that the deleterious effects develop only several hours after the puncture has been made is characteristic of both types of cones, perhaps more of the upper. Even with tonsillar (cerebellar) herniation, a fatality after lumbar puncture is rarely instantaneous, and death may not follow for several hours. In some instances all that happens is pronounced deterioration in the patient's condition, dating from the puncture. There is no point in illustrating these facts, as they concern the tonsillar cone, by clinical

15. Traquair, H. M.: An Introduction to Clinical Perimetry, St. Louis, C. V. Mosby Company, 1927.

16. McConnell, A. A.: Ventriculography as an Aid in Localization of Intracranial Tumours, Brit. M. J. **2**:796 (Nov. 3) 1923.

records, for they are no doubt familiar to all neurologists. It will be worth while to furnish one or two examples of what happens after lumbar puncture in patients who have temporal herniations, for these are not as well known. Death results from interference with the subthalamic autonomic vegetative centers or with the pathways from them. Before the discovery of these centers, the only clearly envisaged method of death in cases of high pressure was that by medullary anemia and paralysis. Had that doctrine been true, few patients with supratentorial tumor should have died, or it should at least have been simple to save them. Since it has been learned that all the bulbar centers are rerepresented at a higher level, an easier explanation has been found for the facts as they were forced on one. Thus, Oljenick noticed that patients with tumors of the temporal lobe are more apt to die after the ventriculographic procedure than those with tumors elsewhere, a fact which he attributed to the greater possibilities of "shift" when the tumor lies lower than the free edge of the falx. Probably most of these patients had a temporal pressure cone, and the vegetative storm was caused by its pressure. It will be seen, however, that although a cone is more commonly present in cases of temporal tumors than in others, it can, nevertheless, occur wherever the tumor lies, and irrespective of its histologic structure.

Apart from these dangerous effects, the tentorial cone can infuse important alterations into the clinical picture. Take as an example the pyramidal signs in cases of tumor of the temporal lobe. In the majority of cases the paralysis that results is most marked in the face and may be slight in the arm and leg. This is caused by the upward pressure of the tumor on the face area, or more usually on the motor fibers sweeping inward to the internal capsule. In other cases, the degree, the extent and the quality of the contralateral paralysis give rise to comment—the arm and leg as well as the face being very weak, with a heavy tonic overload (fig. 4). This indicates pressure on the crus, which becomes still more certain if there are stiffness of the neck, nuchal pain and anisocoria. In other cases, bilateral rigidity, which may attain a remarkable degree, may be present, as will be recorded in a case. Again, the cause is compression of the midbrain. In a recent case in which a meningioma weighing 138 Gm. was removed from the temporal fossa, bilateral extensor plantar responses were present, to disappear after the successful removal of the tumor. It is certain that this meningioma, large though it was, did not actually compress the front of the crura. The bilateral extensor reflexes were due to transmitted pressure at the tentorial level. For the purposes of this paper, it has been necessary to illustrate the anatomic relations of this pressure cone chiefly with autopsy material. In many cases this cone can, none the

less, be successfully treated, with recession of the hernia, as in the case just cited (and in another to be recorded more fully, in which the hernia was removed). The cone may occur with tumors at a distance from the temporal lobe. Thus, a tumor which cannot by its own local action influence tonus of the limbs may yet do so by crowding the brain into the incisura tentorii (case 2). The Kernohan-Woltman crescent will be thought of as an equally possible cause, but it is my impression that the cone is a much commoner one. Moreover, when it is unilateral and of long standing it will cause a cut in the exposed crus of the opposite side by pressing it against the tentorium.

Anisocoria as a sign of compression of the midbrain associated with the cone is illustrated in case 4. Dilatation of the ipsilateral pupil has been observed in a case of frontal astrocytoma, in which it appeared

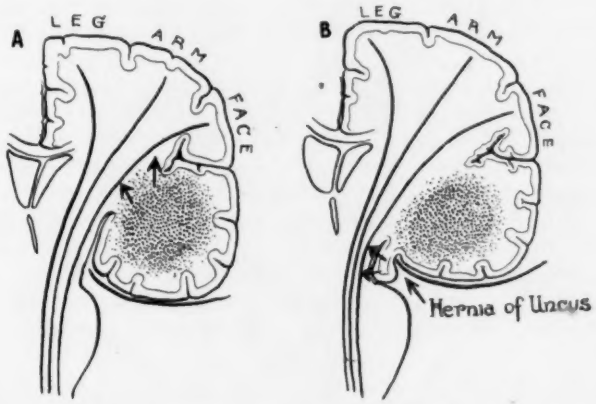


Fig. 4.—Diagrammatic representation of the effects of the cone on contralateral pyramidal signs.

coincidentally with the high peaks of severe headache and disappeared after a successful lobectomy. Since this paper was written, Reid,[17] working in Penfield's clinic, successfully produced the cone experimentally in monkeys and, after several hours of compression, demonstrated dilatation of the ipsilateral pupil. He showed that the herniated uncus comes to press on the oculomotor nerve, though it is still uncertain whether the pupillary change is central or peripheral. The later observations of Smyth and Henderson have attested to the truth of this statement. The cone not only plugs the tentorium but reduces the posterior end of the third ventricle to a narrow slit.

17. Reid, W.: Communication at a meeting of the Neuro-Surgical Society, Montreal, Canada, June 1937.

Lastly, it seems certain that herniation of the incisura, its plugging with tissue of the temporal lobe, must interfere with the extracerebral return of the cerebrospinal fluid into the hemispheral chamber and must be one cause of the interesting phenomenon of ventricular dilatation associated with hemispheral tumors.

REPORT OF CASES

CASE 1.—*Right parietal astrocytoma with cyst formation. History of fits for six years; left hemiplegia for two years; lumbar puncture; death on next day; tentorial pressure cone.*

History.—C. L., a man aged 30, was admitted to the neurosurgical service of the Manchester Royal Infirmary, on July 18, 1936, having been referred by Dr. Fergus Ferguson. Six years previously, he had begun to suffer from epileptic fits, commencing with an abdominal aura of hypothalamic type and followed by myoclonus in the left hand, which spread to the shoulder and face. This lasted two minutes; sometimes he had diplopia before he became unconscious. Originally, for the rest of the day he had postepileptic palsy of the arm and leg. During the past two years the transitory palsy had become more profound; he walked now with a hemiplegic gait, and the left arm was to all intents, useless. He had suffered from headaches at times during the last four years, but for twelve months, especially for the last three months, they had become exceedingly severe. Some were observed in the hospital; the onset was abrupt; he writhed in bed, beating his head on the pillow and banging his forehead with his hand. He could scarcely speak during the headache, describing it as terrible and located at the vertex. There had been dyspnea on exertion for the past twelve months. Micturition was normal. There were no uncinate attacks. He had had attacks of diplopia, usually at monthly intervals, lasting for a few minutes, but he could not amplify this statement intelligently, except to say that he had proved the right eye to be at fault.

Examination.—The optic nerve heads were no more than mildly congested, with no measurable edema. Pupillary reactions were normal. He had left hemiparesis, with no hand grip; he walked with difficulty. There were marked hypertonicity and left hemianesthesia of cortical type, but cooperation was poor and he often gave manifestly impossible answers. The visual fields seemed normal, but were unreliable. There was a swelling, 2.5 cm. in diameter, 1 inch (2.54 cm.) to the right of the midline, suggesting hyperostosis over a meningioma, but roentgenograms showed no increased vascularity; instead, there was a little thinning at this point. There were also a few faint linear calcifications, suggesting a parietal astrocytoma.

Course.—While in the hospital the patient had four generalized fits, with the old abdominal aura and a feeling of tension in the paralyzed left arm.

Diagnostic Comment.—The history and clinical findings were indicative of a tumor in the right parietal area. The severity of the headaches, in paroxysmal attacks, suggested acute intermittent cerebrospinal fluid block, and more advanced changes in the nerve heads had been expected. However, with a tumor high in the right parietal area it was difficult to see how such a block could come about. The bony swelling, associated with the roentgenographic findings, was strongly in favor of a benign glioma. The mental changes were peculiar, lack of interest suggesting the high intracranial pressure which often produces signs of frontal

involvement. The paradox of these alterations and the near normal optic nerve heads was thought to call for a routine reading of the lumbar pressure, though the violence of the headache should have been a warning.

Lumbar Puncture and Subsequent Course.—On July 26, in the afternoon, a lumbar puncture was performed. Pressure was 320 mm., and the protein content, 20 mg.; globulin was not increased; no cells were seen. Within a few hours there developed severe headache, of vertical type familiar to the patient, and he passed a very restless night. At noon the next day he became comatose. The neck and arms were not notably rigid, but the abdomen and legs were in extreme extensor hypertonus, so that they could scarcely be bent. Occasionally he had decerebrate attacks, with stertor and rigidity of the neck and

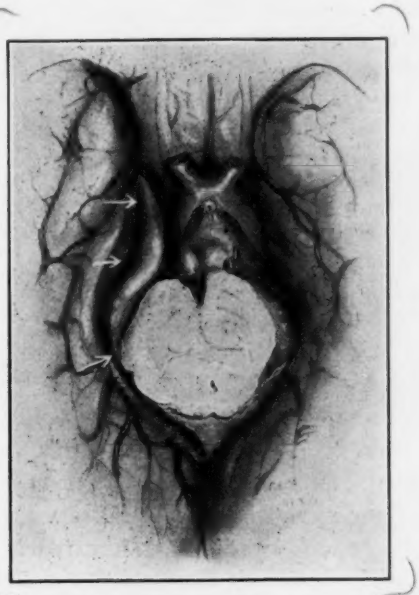


Fig. 5 (case 1).—Severe pressure cone in a case of parietal cystic astrocytoma.

adduction of the arms. He died the same evening, in spite of vigorous, if nonoperative, treatment.

Autopsy.—A cystic glioma, with a shaggy neoplastic lining, was observed beneath the precentral gyrus. Examination of the base of the brain revealed that a large pressure herniation had arisen from the inner surface of the right temporal lobe (fig. 5). The deformity of the midbrain and the slight flattening of its right side can be seen in the drawing (fig. 5).

This unfortunate end taught a lesson; there was the meager consolation that the tumor lay in a situation where its most successful treatment would have left the patient completely hemiplegic. The special difficulty in the management in this case lay in the presence of high intracranial pressure with negligible changes in the disks.

The next example illustrates the late development of hemiparesis caused by a pressure cone, the tumor being so far anterior that it could not have compressed the motor area or the corona radiata. The Kernohan-Woltman crescent was absent.

CASE 2.—*Right frontal meningioma; five years' history of general symptoms and one month's history of left hemiparesis, coinciding with onset of semistupor; no operation; death; bilateral pressure cone.*

History.—L. J., a woman aged 43, gave a history of lack of concentration and unsettled state, with constant change of employment for five years. Four years ago the right breast had been amputated for a duct carcinoma. There was a history of headache for six months. For one month there had been complete apathy and weakness of the left arm.

Examination.—The patient was semicomatose and incontinent on admission; she could not feed herself, and the mouth was dirty. The pupils were both dilated; the reactions to light were feeble enough to call for comment at the time of examination. There was low grade papilledema. Convergence could not be tested, nor the fields taken. The tendon reflexes were extremely active on both sides in both the arms and the legs; there was hypertonus in both legs, with an extensor plantar response and ankle clonus bilaterally. The pulse rate varied from 88 to 106.

Course.—The patient died in spontaneous hyperthermia on the third day after admission, without operation.

Autopsy.—A right anterior parasagittal meningioma, weighing 120 Gm., was observed. There was a bilateral pressure cone extending into the incisura tentorii (fig. 2 *C*).

This was an interesting case clinically. Duct carcinoma does not often metastasize to the brain, so that it was presumed that the unquestioned intracranial tumor was an independent new growth. This proved to be the case. The general condition of the patient was too poor to allow an operation. The increased tendon reflexes and the hypertonicity of both lower limbs were striking findings in a patient in such a vegetative state. There ought to have been a local lesion to explain this, as indeed there was—not the tumor but the tentorial pressure cone. The defective pupillary reactions were no doubt due to the same cause.

The next case is one of the most interesting of the series. It represents one of the unexpected fatalities which are so disturbing and leave all those concerned with many regrets. However, something of scientific importance can often be salvaged from disaster, and here it is possible to demonstrate both the tonsillar and the temporal pressure cone, the coexistence of which was foreshadowed on an earlier page.

CASE 3.—*Meningioma of the right temporal fossa. First stage operation; sudden death.*

History.—C. W., a woman aged 47, was admitted to the neurosurgical service of the Manchester Royal Infirmary, complaining of headaches and severe pain in the back of the neck. She had suffered from headaches at times during her life, but in August 1936 she commenced to have them in the occipital region. They

lasted for three or four hours and were throbbing in character and so severe that she felt like banging her head on the wall. She thought suicide justifiable as an escape from such pain. The headaches were accompanied by vomiting, often two or three times a day. The pain had a strong tendency to radiate into the neck and make it stiff. Lately, she had rarely been free from nuchal pain, and it is noteworthy that her dominant complaint when her history was taken was pain in that situation. She had had a nontoxic goiter for many years, and in December 1936 hysterectomy had been performed for uterine fibroids; since, vision had deteriorated, and she was drowsy and tired. She had impressed her relatives as being forgetful and apathetic, but she gave the history of her illness without difficulty. She had the odd mixture of Witzelsucht and concern about her condition that many patients with tumor of the frontal lobe present. Uncinate attacks were absent.

Examination.—The only objective findings were high grade bilateral papilledema without field defect, expressional palsy of the left side of the face and 75 mg. of albumin in the cerebrospinal fluid. Pupillary reactions were normal, and there was no hypertonus. Roentgenograms were normal.

Course.—While under observation the patient improved, and, in spite of the short history, it seemed that the tumor might be benign. Lumbar puncture was performed twice, without incident.

Presumptive Diagnosis.—The diagnosis was tumor, possibly meningioma, of the right frontal or anterior temporal region.

Operation.—On April 20, 1937, ventriculograms revealed a right temporal tumor. An osteoplastic flap was immediately turned down on the right side, with the patient under anesthesia induced with avertin and nitrogen monoxide and oxygen administered intratracheally by a competent anesthetist. Shortly after the flap was outlined, the intratracheal tube became displaced and soon came out, making it difficult to continue the operation, owing to congestion, embarrassed respiration and cyanosis. The goiter interfered with respiration. The dura was as tight as a drum, and ventricular puncture failed to reduce its tenseness. It was thought wiser not to open the dura but to cut the session short, reopening the incision in a day or two.

This program turned out badly, for as the skin was being closed breathing became increasingly stertorous and the pulse intermittent. The patient died an hour later.

Autopsy.—A large soft meningioma, filling the right middle fossa, was observed. It had eroded into the tegmen tympani, but its removal should not have presented great technical difficulty.

Why had this woman so incontinently and unexpectedly died? Examination of the basal surfaces of the brain gave the answer, for there was a double pressure cone, one into the hiatus tentorii and the other into the foramen magnum (fig. 6). Of the two, the superior was much the larger and probably the more important, though the combined action of the two must have been formidable. It will be remembered that the patient had had two lumbar punctures and survived them, in spite of nuchal pain as an aggressive feature. The anesthetic difficulties were the determining factor in this case, but the true etiologic cause of death was the double pressure cone. The paroxysmal headaches and the nuchal

pain and rigidity portended great danger, and probably once things began to go wrong they could not have been rectified.

Paradoxic diencephalic signs of a type characterized by decerebrate rigidity may be present when evidence of a tumor of the temporal lobe is clinically clearcut. Rigidity of the neck and limbs may then lead to doubt as to the nature of the lesion, for these signs can be so "meningeal" in their quality that the observer believes (wrongly, as things turn out) that he is dealing with a leaking cerebral abscess. Nuchal rigidity

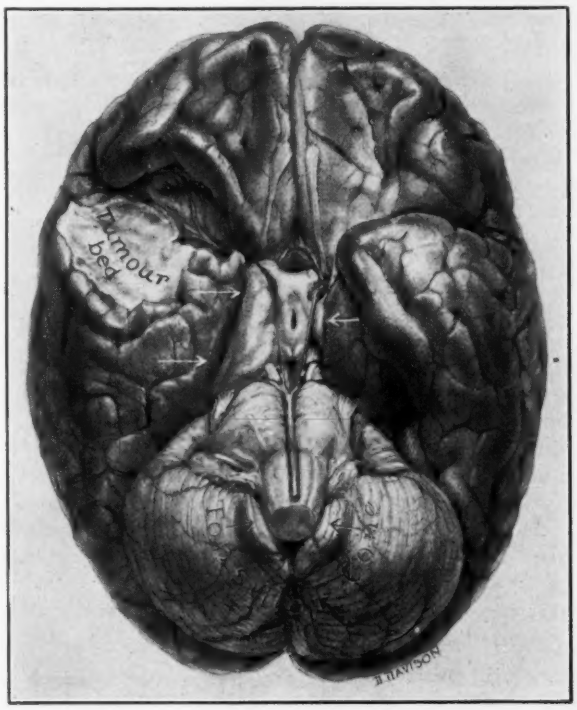


Fig. 6 (case 3).—Tonsillar and temporal pressure cones in a case of meningioma of the right basal temporal region.

can be a striking feature of some aseptic supratentorial lesions (apart from subarachnoid bleeding), and I still recollect my puzzlement on first meeting it several years ago in a child with a large suprasellar cyst arising from the pituitary anlage.

In the next case the evidences of compression of the midbrain were well defined and were recognized at their true value, with a favorable result.

CASE 4.—*History.*—J. D., a man aged 28, was referred to the neurosurgical service of the Manchester Royal Infirmary by Dr. H. G. Garland, of Leeds, on Nov. 16, 1936. He had had tonsillectomy twelve months before for relief from

chronic sepsis and rheumatism. Aside from that, he had been well. Two months before admission he came home complaining of severe attacks of vertigo and frontal headache. After a week's rest he returned to work and continued until two weeks ago, when the headaches recurred and made it impossible for him to go on. He vomited for three days, when he was taken into a hospital by Dr. Garland. During the past two months he had become irritable and touchy in his family contacts. On admission, Dr. Garland found papilledema bilaterally; the visual fields were normal, but cooperation was poor because of drowsiness, and pain interfered with attention. The patient was disoriented for time and place. He could not remember his birthday or the name of the king, but admitted that he should have known them and had forgotten. There was a doubtful history of nasty tastes, but the tongue was furred and the breath rather foul.

A lumbar puncture was done; the pressure was 300 mm. of water, with rapid fluctuations and pronounced respiratory oscillations. Five cubic centimeters of fluid was removed; it contained 10 lymphocytes and 80 mg. of protein; the Lange colloidal gold curve was normal, and the Wassermann reaction was negative. After lumbar puncture the drowsiness increased rapidly, and within forty-eight hours Dr. Garland found the patient almost comatose. He made the interesting observation that both pupils had now become fixed to light and the left plantar response had become sharply extensor. At this point the patient was transferred to my service.

Examination.—The patient lay in bed with the eyes closed, but had sudden attacks of restlessness. He had taken off the bandage applied when the head was shaved. The hands were moving constantly, and he looked as if he should answer when spoken to. Actually, he answered in a dreamy sort of way, better than one would have expected from watching his behavior, and he cooperated within limits. The right pupil was now found to be dilated and fixed; the left pupil measured 4 mm. and was also fixed to light. He preferred to keep his eyes closed. There was a constant tremor of the right hand as he picked at the bedclothes. The arm was found to be rigid at the shoulder joint, less so at the elbow. The left arm was so strongly flexed and adducted against the chest that it could scarcely be pulled away. The abdomen presented an unusual picture. It was retracted and stiff, like that in tuberculous meningitis; there were no abdominal reflexes. Both legs were half flexed and very rigid, so that a good deal of power was needed to straighten them. The knee jerks were difficult to obtain, owing to the hypertonus. The left ankle was remarkably rigid, so that tests for ankle clonus were unavailing. The left plantar reflex was extensor, and the right, indeterminate. Kernig's sign was elicited, but distinctly more on the left than on the right, suggesting a cerebral rather than a spinal root origin for the rigidity. The neck was extremely rigid, and the patient complained when an attempt was made to flex the head. The blood count was 20,000 white cells, 75 per cent polymorphonuclear cells and 20.5 per cent lymphocytes. The temperature varied from 97 to 99 F., and the pulse rate, from 60 to 90.

Diagnostic Comment.—The short history and the high leukocyte count suggested a cerebral abscess, probably in the right temporal lobe because of the mydriasis on that side. The rigidity of the four limbs, the stiffness of the neck and the remarkable rigidity and retraction of the abdomen suggested meningitis; yet the general state of well-being and the relatively slow pulse were both against infection. It was thought that the explanation would probably be found in a lesion of the right temporal lobe with a tentorial pressure cone. The pre-

operative diagnosis, none the less, was abscess. This was wrong; the lesion was an isomorphic glioblastoma, with well formed blood vessels.

Operation.—On November 20, with avertin, general anesthesia induced by intratracheal administration of nitrogen monoxide and oxygen and local anesthesia with procaine hydrochloride (the method used as a routine in the service), the right temporal lobe was exposed. On opening the dura and puncturing the right temporal lobe, resistance was met at a depth of 2 cm. A cone of the temporal lobe, measuring 4 cm., was excised, uncapping a reddish tumor. This was punched away with a diathermy pituitary rongeur forceps, and afterward the endotherm cutting loop was employed. It seemed imperative to make as extensive a removal as possible because of the signs of involvement of the midbrain. The temporal lobe was punched, looped and sucked out from its anterior pole backwards, baring the floor of the middle fossa up to the edge of the incisura tentorii. The midbrain could now be seen clearly (fig. 7). There was now no

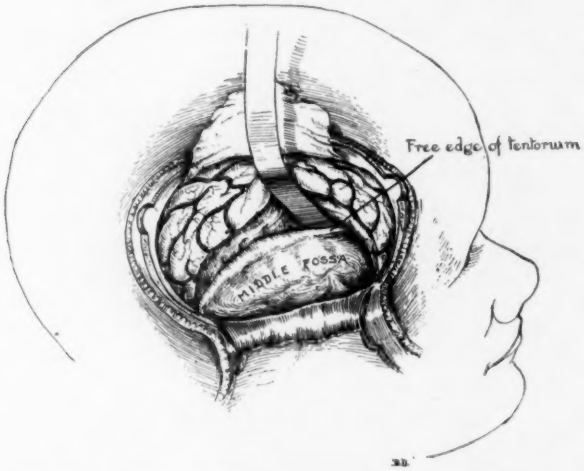


Fig. 7 (case 4).—Sketch of the operative field after excision of the temporal lobe for glioblastoma.

pressure at all; the brain was slack and fell away from the dura. The large empty cavity was filled with Ringer's solution and tight closure carried out.

Course.—On the next day the rigidity had completely disappeared; the abdomen was normal; tone was normal in the limbs on both sides, and voluntary power was excellent, proving that the whole picture of rigidity had been produced by compression of the diencephalon. From that time, the patient made complete recovery, causing not the least anxiety. The mydriasis of the right pupil persisted, as it will for some time after evacuation of an extradural clot. The reactions of the left pupil returned on the next day. The patient had no recollection of any events during the past two weeks or of the hospitals in which he had been.

This was a fascinating case. It is satisfactory to have another rational explanation for signs which are alien to those which the main

focal lesion would be likely to produce by purely cortical or subcortical neuronal disruption.

DECEREBRATE RIGIDITY

The last case brings up the question of decerebrate rigidity and a possible mechanism for its production in man. A transverse physiologic block at the level of the tentorium would be in exactly the right location to produce it. Several years ago, there was considerable interest in the decerebrate state, stimulated chiefly by a paper by Kinnier Wilson.[18] It happened that at that date I saw and put on record 2 cases of acute decerebration produced by massive middle meningeal hemorrhages.[19] In the first case the following note was made:

> He lay flat upon his back, the arms rigid and extended by the sides. The hands were half clenched, and the forearm hyperpronated, so that the backs of the hands were facing the outer aspects of the thighs. The legs were stiffly extended and the toes pointed downwards, the ankles being strongly plantar flexed and slightly inverted. The muscular rigidity was so great that considerable force was necessary to bend the limbs. Any attempt to alter the position in which the limbs lay seemed to bring on an excess of tonic rigidity, a fine tremor then appearing. The patient's head was turned sharply to the left, as were the eyes; the neck was rigid and the chin a little lifted, but no opisthotonos appeared. Cheyne-Stokes breathing was present, and at the height of the noisy, rattling respiration the tonus was exaggerated, the arms becoming even more pronated, and the legs more rigid and adducted, the feet remaining in extreme plantar flexion. . . . The left pupil was widely dilated.

I was not as certain then as I am now that this intense four limb rigidity is the human equivalent of the decerebrate cat's state. Since that date, a few other cases of decerebrate rigidity have been encountered, as the result either of tumor or of craniocerebral injury. The most interesting are those in which the cause is extradural hemorrhage, with the brain intact, as in the 2 cases recorded in 1921,[15] for there is less possibility of invasion of the tumor to blur the clarity of causation. The picture becomes still more striking and provocative of thought when a decerebrate state is linked with pupillary alterations, such as the hutchinsonian pupil. It cannot be doubted that a pressure cone develops in these cases and produces acute decerebration. Whether the cone is the only means by which decerebration occurs is another matter, for jacksonian cerebellar tonic fits come to mind and one wonders whether anemia alone may not be a reason. However that may be, it seems on the face of it extremely probable that the tentorium is the level of decerebration in all proper cases.

---

18. Wilson, S. A. K.: On Decerebrate Rigidity in Man and the Occurrence of Tonic Fits, Brain **43**:220 (Nov.) 1920.

19. Jefferson, G.: Bilateral Rigidity in Middle Meningeal Haemorrhage, Brit. M. J. **2**:683 (Oct. 29) 1921.

CONCLUSIONS

Whether one adopts the term tentorial pressure cone or temporal pressure cone is a matter of small moment. The important thing is to know that it exists, that it produces recognizable and, I believe, curable phenomena, such as have been illustrated here. The cone must be of fairly common occurrence, but in cases in which intervention is successful it must recede spontaneously with the shrinkage of the brain volume which occurs after removal of the tumor, but not so materially after decompression. This may explain the disappointing results in many cases of pure decompression.

The case histories and the pathologic evidence presented show clearly the dangers which this pressure cone can introduce into intracranial dynamics. I believe that lumbar puncture should be withheld in cases of high pressure, even if the lesion is known to be hemispheral, unless it is believed to be essential to the diagnosis. However, one must go further and add that the changes in the optic nerve head are not to be taken as the sole criterion of the degree of pressure; there may still be danger if there is paroxysmal headache and if there are signs, such as have been discussed, that indicate compression of the midbrain. If any puncture is needed, it should be ventricular. It seems that in this pressure cone there is an explanation of some, if not all, of the fatalities after ventriculographic study not followed by immediate operation, or followed by a first stage operation without opening the dura.

Last, the shadings, the variabilities and the nuances of the clinical picture which can be induced by pressure of the uncus on the crus cerebri can be better evaluated if the observer is alive to the possibility of this complicating factor. He will know that not all fixed and anisocoric pupils indicate a tectal or pineal tumor; he will look with a more understanding eye on diencephalic signs, and he will seek by operation to undo, as best he can, the mischief that the cone produces.

PHYSICOCHEMICAL PROPERTIES OF BRAIN, ESPECIALLY IN SENILE DEMENTIA AND CEREBRAL EDEMA

DIFFERENTIAL RATIO OF SKULL CAPACITY TO VOLUME, SPECIFIC WEIGHT, WATER CONTENT, WATER-BINDING CAPACITY AND p_H OF THE BRAIN

LEO ALEXANDER, M.D.
AND
JOSEPH M. LOONEY, M.D.
WORCESTER, MASS.

It has been demonstrated by one of us (L. A.),[1] in part in collaboration with Wu,[2] that among the postmortem changes presented by the central nervous system of patients who had suffered from severe gastro-intestinal infections, such as dysentery, cholera and intestinal tuberculosis, there is, in addition to the evidence of circulatory disturbance indication of a diffuse physicochemical alteration of the brain bulk, which is associated with, and is probably the underlying cause of, certain structural changes. Our main observations concerning this point were: (1) pseudoatrophy; (2) alteration of the water-binding capacity of the brain tissue, as expressed by the rate of swelling in various solutions of sodium chloride, acid and alkali and by swelling or shrinkage in fixation fluid, and (3) a peculiar change in the response of the tissue to silver salts. The last had already been observed by other authors, who interpreted it as analogous to that of tissue which had undergone senile cellular changes. A somewhat similar, but not identical, change could be produced experimentally by soaking fresh human brain tissue in water or saline solutions before fixation.

Before and at the same time, von Braunmühl [3] emphasized the importance of physicochemical changes (swelling and precipitations) in

---

From the Research Department of the Worcester State Hospital and the Memorial Foundation for Neuro-Endocrine Research.

1. Alexander, L.: Neurofibrils in Systemic Disease and in Supravital Experiments, with Remarks on Pseudo-Atrophy of the Brain, Arch. Neurol. & Psychiat. **32**:933 (Nov.) 1934.

2. Alexander, L., and Wu, T. T.: Cerebral Changes in Gastro-Intestinal Infections with Terminal Cachexia, Arch. Neurol. & Psychiat. **33**:72 (Jan.) 1935.

3. von Braunmühl, A.: Kolloidchemische Betrachtungsweise seniler und präseniler Gewebsveränderungen: Das hysteretische Syndrom als cerebrale Reaktionsform, Ztschr. f. d. ges. Neurol. u. Psychiat. **142**:1, 1932; Synäresis und Ent-

(Footnotes continued on next page)

senile dementia and dementia paralytica; furthermore, Pötzl,[4] Rosenfeld,[5] Reichardt [6] and Medow [7] expressed the opinion that swelling processes of the brain occur also in dementia praecox, which may be due to a chronic and insidious slight deficiency in oxygen supply (Hoskins [8]). All these statements point to the increasing importance of determining the normal and pathologic physicochemical properties of the brain, especially its water relationships. In other fields more advances have been made along these lines. In botany and zoology the determination of the equilibrium of free and bound water, for instance, has gained practical importance, since Newton,[9] Newton and Martin,[10] Gortner,[11] Robinson [12]

zündung: Ueber Versuche einer kolloidchemischen Pathologie zur Klärung grundsätzlicher Fragen einer Paralyseanatomie; dargestellt am Beispiel der Lissauerschen Paralyse, ibid. **148**:1, 1933; Allgemeine Fortschritte der Histopathologie, Fortschr. d. Neurol., Psychiat. **6**:200 (May) 1934.

4. Pötzl, O.: Zur Frage der Hirnschwellung und ihrer Beziehungen zur Katatonie, Jahrb. f. Psychiat. u. Neurol. **31**:244, 1910.

5. Rosenfeld, M.: Zur klinischen Diagnose der Hirnschwellung, Ztschr. f. d. ges. Neurol. u. Psychiat. **53**:235, 1919-1920; Ueber atypische Psychosen, Arch. f. Psychiat. **65**:150, 1922.

6. Reichardt, M.: Zur Entstehung des Hirndrucks bei Hirngeschwülsten und anderen Hirnkrankheiten und über eine bei diesen zu beobachtende besondere Art der Hirnschwellung, Deutsche Ztschr. f. Nervenh. **28**:306, 1905.

7. Medow, W.: Bewusstseinstrübungen bei Dementia praecox, Arch. f. Psychiat. **67**:373, 1922.

8. Hoskins, R. G.: Oxygen Metabolism in Schizophrenia, Arch. Neurol. & Psychiat. **38**:1261 (Dec.) 1937.

9. Newton, R.: A Comparative Study of Winter Wheat Varieties with Especial Reference to Winter Killing, J. Agric. Sc. **12**:1, 1922; The Nature and Practical Measurement of Frost Resistance in Winter Wheat, Edmonton, Research Bulletin 1, University of Alberta, College of Agriculture, 1923, p. 53; Colloidal Properties of Winter Wheat Plants in Relation to Frost Resistance, J. Agric. Sc. **14**:178, 1924.

10. Newton, R., and Martin, W. M.: Physico-Chemical Studies on the Nature of Drought Resistance in Crop Plants, Canad. J. Research **3**:336, 1930.

11. Gortner, R. A.: The State of Water in Colloidal and Living Systems, Tr. Faraday Soc. **26**:678, 1930; The Hydration Capacity of Starch, Cereal Chem. **10**:298, 1933; The Rôle of Water in the Structure and Properties of Protoplasm, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1932, vol. 1, pp. 21-54; Water in Its Biochemical Relationships, ibid., 1934, vol. 3. Gortner, R. A., and Gortner, W. A.: The Cryoscopic Method for the Determination of "Bound Water," J. Gen. Physiol. **17**: 327 (Jan. 20) 1934.

12. Robinson, W.: Water Binding Capacity of Colloids a Definite Factor in Winter Hardiness of Insects, J. Econom. Entomol. **20**:80 (Feb.) 1927; in Weiser, H. B.: Colloid Symposium Monograph, New York, Chemical Catalogue Company, Inc., 1928, vol. 5, p. 199; Response and Adaptation of Insects to External Stimuli, Ann. Entomol. Soc. Am. **21**:407, 1928; Water Conservation in Insects, J. Econom. Entomol. **21**: 897, 1928; Free and Bound Water Determinations by the Heat of Fusion of Ice Method, J. Biol. Chem. **92**:699 (Aug.) 1931.

and others determined it to be an indicator of hardiness to winter and drought in plants and insects. Sacharow [13] found an increase in bound water during hibernation. It may be noted that neurofibrillar changes, similar to those which we noted in cases of intestinal infections with terminal cachexia, were observed in hibernation by Tello.[14] Important data concerning the differential ratio of the capacity of the skull and the volume and specific weight of the brain and the total water content of the gray and white matter were gathered by Rieger,[15] Reichardt,[16] Apelt,[17] Rudolph [18] and Schlüter and Never,[19] but no correlation with the water-binding capacity of the brain has been attempted.

This study includes such physicochemical properties of the brain as the weight and volume and their relation to the capacity of the skull, the specific weight of the brain, the total water content of the gray and the white matter, the p_H, the water-binding capacity and the maximum shrinkage in solutions of sodium chloride. Reference is made to the clinical symptomatology and the gross and microscopic pathologic changes in the cases under consideration.

MATERIAL AND METHODS

This study is based on observations on 22 human brains. The following examinations were made:

1. The capacity of the skull was measured, according to the methods of Rieger,[15] Reichardt [16] and Rudolph,[18] by the amount of water necessary to fill the cranial cavity after removal of the brain. Care was taken by a special device (an adjustable band of sheet iron) to draw a straight line around the skull, in order to attain an ideally even sawing line in opening the skull. Then the calvarium and the base were measured separately. The dura was left in the skull for this determination. The foramen magnum and the outlets for nerves and blood vessels were plugged with plaster of paris. Several (at least two) determinations were made each time, and the mean was taken. If the sawing line was straight, the source of error was insignificant. In this study only the 22 cases were used in which we succeeded in getting a perfectly straight line.

13. Sacharow, N. L.: Studies in Cold Resistance of Insects, Ecology **11**:505, 1930.

14. Tello, F.: Las neurofibrillas en los vertebrados inferiores, Trab. d. lab. de invest. biol. Univ. de Madrid **3**:113, 1904.

15. Rieger, K.: Eine exakte Methode der Kraniographie, Jena, Gustav Fischer, 1885.

16. Reichardt, M.: Ueber die Bestimmung der Schädelkapazität an der Leiche, Allg. Ztschr. f. Psychiat. **62**:787, 1905.

17. Apelt, F.: Der Wert von Schädelkapazitätsmessungen und vergleichenden Hirngewichtsbestimmungen für die innere Medizin und die Neurologie, Deutsche Ztschr. f. Nervenh. **35**:306, 1908.

18. Rudolph, O.: Untersuchungen über Hirngewicht, Hirnvolumen und Schädelkapazität, Beitr. z. path. Anat. u. z. allg. Path. **58**:48, 1914.

19. Schlüter, A., and Never, H. E.: Zur Frage der Hirnschwellung: Physikalische und histologische Untersuchungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:172, 1932.

2. The brain was weighed; the volume was determined by measuring the overflow of water from a tin container with a constant level when the brain was completely immersed.

3. The total water content was measured by the loss of weight of separate pieces of gray and white matter which occurred in drying them to constant weight, at 105 C.

4. The p_H was measured with the quinhydrone electrode, with the aid of the potentiometer. For this purpose, a brain emulsion in neutral physiologic solution of sodium chloride was prepared (1 Gm. of brain substance in 10 cc. of a 0.9 per cent solution of sodium chloride).

5. The water-binding capacity of the brain in distilled water and in solutions of sodium chloride of various concentrations was measured for large cuboid pieces, containing both gray and white matter and weighing from 3 to 8 Gm., in most instances about 5.5 Gm. Within this range the difference in weight does not appreciably alter the shape of the absorption curves. The following concentrations of sodium chloride were used: 0.3, 0.9, 1.2, 1.5 and 10 per cent. Symmetric blocks of fresh tissue were cut from both frontal lobes at autopsy with a sharp razor blade, care being taken to cut straight, flat edges to avoid crumbling of the blocks. The six blocks were weighed, and each was soaked in a different solution, at a temperature of 4 C. The blocks were weighed again at regular intervals, and curves representing the changes of weight in the various fluids, expressed in percentages of the original weight, were plotted. At the time of weighing the preparations had to be removed from the refrigerator, and their temperatures rose to from 13 to 16 C. However, this fact did not interfere noticeably with the slope of the absorption curves.

6. In all cases blocks from area 10, the central region, areas 17, 18 and 19, the cornu ammonis and the area entorhinalis were fixed in solution of formaldehyde U. S. P. (1:10), and frozen sections from these regions were stained with Bielschowsky's silver impregnation method for intracellular neurofibrils. Neighboring blocks were fixed in 95 per cent alcohol and examined with the Nissl method, and in some cases also with the Masson trichrome method and hematoxylin and eosin. In a few cases sections from area 37, the island of Reil, the striatum and the thalamus opticus were also examined. In some of the cases in which neurofibrillar alterations were shown, sections from blocks fixed in 95 per cent alcohol were examined with the microincineration method (Policard,[20] Scott[21] and Alexander and Myerson[22]). Although these histologic data were utilized in the pathologic diagnoses, their detailed description is given in a separate paper.[23]

These determinations offered the following groups of data, which we attempted to correlate with each other: (1) the differential ratio of skull capacity to brain volume, expressed as a percentage of the skull capacity; (2) the differential ratio

---

20. Policard, A.: Sur une méthode de microincinération applicable aux recherches histochimiques, Bull. Soc. chim. de France **33**:1551, 1923.

21. Scott, G. H.: The Localization of Mineral Salts in Cells of Some Mammalian Tissues by Microincineration, Am. J. Anat. **53**:243 (Sept.) 1933.

22. Alexander, L., and Myerson, A.: The Mineral Content of Various Cerebral Lesions as Demonstrated by the Microincineration Method, Am. J. Path. **13**:405 (May) 1937.

23. Alexander, L., and Looney, J. M.: Histopathology of Senile Dementia and Related Conditions, Studied by Silver Impregnation and Microincineration, Arch. Neurol. & Psychiat., to be published.

of skull capacity to brain weight, expressed as a percentage of the skull capacity; (3) the specific weight of the brain; (4) the total water content of the gray matter; (5) the total water content of the white matter; (6) the water-binding capacity and the maximum shrinkage of the brain tissue in water and in various solutions of sodium chloride; (7) the slope of the curve for water absorption, as indicated by the time required to reach a certain level; (8) the p_H of the tissue, and (9) the histologic appearance, especially the neurofibrillar picture. In several instances this could be compared with the appearance of microincinerated preparations.

RESULTS

Our data are presented in the table accompanying, which includes the age of the patient, the clinical and pathologic data and the time after death at which autopsy was performed. Detailed histologic descriptions are given in a separate paper.[23]

1. *Capacity of the Skull.*—The capacity of the skull varied from 1,010 to 1,480 cc. The lowest figure was obtained in a woman (case 28) suffering from Alzheimer's disease; the highest, in a youth (case 13) with schizophrenia.

2. *Weight of Brain.*—The weight of the brain varied from 905 to 1,470 Gm. The lowest weight was found in the severely atrophic brain of a woman (case 28) with Alzheimer's disease; the next lowest (1,110 Gm.), however, was observed in the severely edematous brain of a woman (case 21) suffering from hysteria who had committed suicide by hanging. The two highest weights (1,470 Gm.) were found in 2 men with schizophrenia, 1 of whom (case 16) showed a markedly edematous brain (suicide by lye poisoning), and the other (case 13) a moderately atrophic brain. This illustrates the fact that the weight of the brain alone cannot be used as an indicator of atrophy and edema.

3. *Volume of Brain.*—The volume of the brain varied from 820 (in case 6, of Pick's disease) to 1,415 cc. (in case 16, of cerebral edema). However, even the brain volume in itself does not show sufficient correlation with the presence or absence of edema or atrophy to be used as an indicator. These conditions can be measured only by the differential ratio of the capacity of the skull to the volume or weight of the brain.

4. *Differential Ratio of Skull Capacity to Brain Volume ("Differential Ratio").*—This ratio is determined as the difference between the skull capacity and the brain volume, expressed as the percentage of the skull capacity. This ratio varied from + 29.31 (in case 6, of Pick's disease with severe atrophy) to —7.83 per cent (in case 32, of nephrosclerosis with cerebral edema). This differential ratio was high for atrophic brains and low, zero or negative for swollen brains. The normal range was from 4 to 9 per cent. Any ratio below 4 per cent expressed edema; any above 9 per cent indicated atrophy. The occurrence of negative values in cases of severe cerebral edema is explained by the

Data on Cases Studied

Case No.	Clinical and Pathologic Data	Postmortem Period, Hr.	Skull Capacity, Cc.	Brain Volume, Cc.	Brain Weight, Gm.	Differential Ratio of Skull Capacity to Brain Volume, %	Differential Ratio of Skull Capacity to Brain Weight, %	Specific Weight of Brain	Water Content of Gray Matter, %	Water Content of White Matter, %	p_H	Preabsorption Time, Hr.	Maximum Shrinkage, %
6	Woman aged 72; senile dementia with focal cortical atrophy (Pick's disease); carcinoma of left breast with metastases to lungs	16	1,160	820	.....	29.31	....	.....	87.22* 82.52†	.....	....	110* 25†	12.4* 2.0†
9	Woman aged 35; dementia praecox, catatonic type; pulmonary intestinal and meningeal tuberculosis; subdural hematoma over left hemisphere; emaciation	2	1,170	1,060	1,160	9.40	0.85	1.094	85.03	67.22	....	...	7.2
10	Man aged 65; dementia praecox; arteriosclerosis involving aorta, cardiac valves and kidneys; frontal convolutions somewhat narrower than usual	11	1,460	1,360	1,380	10.96	5.48	1.062	84.06	70.41	6.55	100	7.1
11	Woman aged 76; psychosis and parkinsonian syndrome with cerebral arteriosclerosis; generalized arteriosclerosis	15½	1,360	1,240	1,345	8.82	1.10	1.085	84.92	69.23	6.45	40	4.0
12	Man aged 66; psychosis with cerebral arteriosclerosis; convulsive seizures; adenocarcinoma of the prostate with metastases (grade IV); bronchopneumonia	57	1,330	1,300	1,400	2.26	—5.26	1.077	85.96	67.33	....	...	...
13	Youth aged 19; schizophrenia; pulmonary, enteric, mesenteric and peritoneal tuberculosis; amyloid degeneration of spleen and liver; gyri of frontal lobe narrow, sulci wide (pseudoatrophy)	48	1,480	1,340	1,470	9.46	0.68	1.097	87.12	70.04	7.00	72	7.1
14	Woman aged 42; psychosis with syphilitic meningoencephalitis; subdural hematoma	17	1,290	1,175	1,220	8.91	5.43	1.038	85.03	68.29	....	..	...
15	Man aged 70; Korsakoff's psychosis associated with chronic alcoholism; generalized arteriosclerosis; frontal convolutions narrow, sulci wide; hemorrhagic softening in right putamen and right caudate nucleus	19	1,365	1,200	1,270	12.09	6.96	1.058	85.09	71.19	6.10	64	3.3
16	Man aged 29; dementia praecox, paranoid type; death from suicide twelve hours after poisoning with household lye; severe burns of face, mouth, trachea, bronchi, esophagus and stomach; perforation of esophagus; hemorrhagic mediastinitis; pulmonary edema; cerebral edema; gyri flattened, sulci reduced to lines	13	1,400	1,415	1,470	—1.07	—5.00	1.039	84.38	67.72	7.19	0	0
17	Man aged 71; parkinsonian syndrome; generalized arteriosclerosis; generalized cortical atrophy, most marked in frontal lobes; hydrocephalus internus (ex vacuo); central white matter atrophic, markedly decreased in amount	2	1,465	1,285	1,330	12.29	9.22	1.035	84.02	70.65	6.52	53	3.8
18	Woman aged 61; dementia praecox, catatonic type; generalized arteriosclerosis, hypertension, nephrosclerosis; subarachnoid hemorrhage, covering base and convexity on both sides, from ruptured aneurysm of basilar artery; frontal convolutions somewhat narrower than usual, others flattened	29	1,350	1,335	1,380	1.11	—0.96	1.034	84.75	69.33	6.59	..	4.6

20	Woman aged 24; dementia paralytica; paralytic seizures; death after series of seizures; infarction of lungs; syphilitic mesaortitis	7	1,266	1,185	1,225	6.40	3.24	1.034	.....	.....	....	..	...
21	Woman aged 36; psychoneurosis, hysteria; suicide by hanging; death after forty-five minutes; subpleural petechial hemorrhages; congestion of the kidneys; cerebral edema; gyri flattened, sulci reduced to lines	9	1,050	1,070	1,110	—1.90	—5.71	1.037	85.70	70.06	6.95	53	4.5
23	Woman aged 75; senile psychosis; generalized arteriosclerosis; coronary atheromatosis; bronchopneumonia; cerebral atrophy, especially of frontal, central and parietal regions	3	1,345	1,190	1,245	11.52	7.43	1.046	83.80	69.41	6.50	25	3.1
24	Man aged 65; psychosis, with cerebral arteriosclerosis; seizures; generalized arteriosclerosis; coronary occlusion; atrophy, especially of frontal lobes; small focus of softening in left red nucleus and in basal part of optic thalamus	14	1,405	1,260	1,345	10.32	4.27	1.067	84.71	70.59	5.81	..	...
27	Man aged 45; imbecility, with congenital spastic diplegia; death from intestinal obstruction (operation) two day after onset; dilatation and early perforation of the descending colon; bronchopneumonia; atrophy of frontal convolutions; marked hydrocephalus internus, with destruction of the septum pellucidum; marked thinning of both internal capsules	7	1,370	.....	.....	.....	....	.....	85.29	70.17	6.62	..	...
28	Woman aged 74; senile dementia (Alzheimer's disease)	2	1,010	870	905	13.86	10.40	1.040	84.30	71.72	....	..	...
29	Woman aged 74; schizophrenia; generalized arteriosclerosis; slight atrophy of frontal convolutions; slight generalized dilatation of ventricles	58	1,270	1,140	1,200	10.24	5.51	1.053	86.48	80.06	....	..	...
30	Man aged 72; chronic paranoid psychosis associated with chronic alcoholism; polyneuritis with weakness, ataxia and areflexia of both legs; history of Jamaica ginger (triorthocresyl phosphate) poisoning five years ago; coronary sclerosis and occlusion; atrophy of frontal lobes; degeneration of anterior horns of lumbar portion of cord	4	1,455	1,235	1,320	15.12	9.28	1.069	83.90	70.81	6.83	..	...
31	Man aged 34; manic-depressive psychosis; gastric ulcer with hemorrhage; brain pale, in other respects of normal appearance	20	1,320	1,270	1,335	3.79	—1.14	1.051	85.91	67.92	....	54	3.5
32	Woman aged 40; psychosis resulting from cardiovascular and renal disease; seizures with tonic rigidity; chronic nephritis, hypertension and pseudouremia; (nonprotein nitrogen 29 mg., later 42 and 45 mg.); nephrosclerosis, hepatitis, hypertrophy of the heart; cerebral edema; gyri flattened, sulci reduced to lines; hemorrhagic softening in left occipital lobe	17	1,085	1,170	1,175	—7.83	—8.29	1.004	85.27	76.04	6.53	36	2.2
33	Woman aged 44; mental deficiency with psychosis; arteriosclerosis, hypertension, chronic nephritis; moderate cerebral edema; gyri of centroparietal, temporal and occipital regions flattened, sulci narrow; in frontal region, gyri narrow	7	1,305	1,290	1,315	1.15	—0.77	1.019	84.83	65.70	6.50	39	3.4

* Severely atrophic areas.
† Less atrophic areas.

increase in volume which such brains undergo after opening the capsule of the skull and the dura—an observation familiar not only to the neurosurgeon but also to the pathologist.

5. *Differential Ratio of Skull Capacity to Brain Weight ("Differential Weight").*—This ratio is the difference between skull capacity (in cubic centimeters) and brain weight (in grams), expressed as the percentage of the skull capacity. It varied from + 10.4 (in case 28, of Alzheimer's disease) to —8.29 per cent (in case 32, of cerebral edema). The normal range was from 0 to 5.5 per cent. The figures obtained were well correlated with the differential ratios of skull capacity and brain volume, in spite of the differences in specific weight (chart 1).

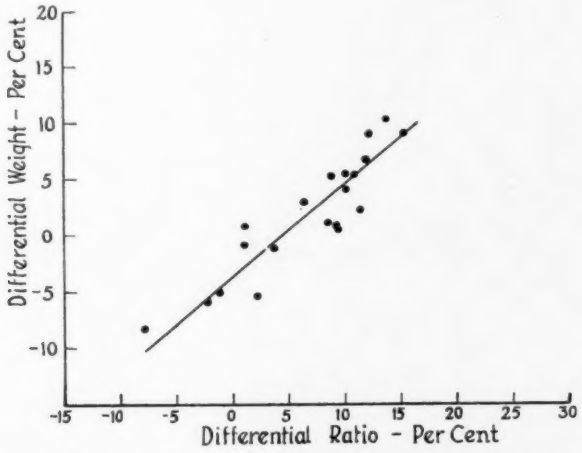


Chart 1.—Comparison of the differential ratio of skull capacity to brain weight (ordinates) with that of skull capacity to brain volume (abscissas) in 20 cases. Notice that one can be fairly well predicted from the other, according to the equation given in the text.

Statistically, r = 0.93, and the differential weight = —3.58 + 0.836 (differential ratio); that is, for each 5 units in the differential ratio of skull capacity to brain volume there was an increase of approximately 4 units in the differential ratio of skull capacity to brain weight. The equation is good enough to predict one variable from knowledge of the other variable. The error of prediction was ± 2 units of differential weight.

6. *Specific Weight.*—The specific weight varied from 1.004 (in an edematous brain, case 32) to 1.097 (in a moderately atrophic brain, case 13). In the majority of cases the specific weights were between 1.030 and 1.070. Although there is no definite correlation of specific weight and atrophy or edema, as expressed by the values for differential ratios, the specific weights, when plotted against the differential ratios,

tend to arrange themselves along a paraboloid curve (chart 2), from which it can be seen that most edematous brains showed specific weights below 1.040 while most atrophic brains showed values above 1.040.

7. *Total Water Content of the Cortical Gray Matter.*—This varied from 82.52 to 87.22 per cent. The range was remarkably small, the majority of values being between 84 and 86 per cent. The highest value observed was in the atrophic cortex in a case of Pick's disease; the lowest, in the less atrophic areas of the same brain. There was no correlation of the water content of the gray matter with either atrophy or edema; both the lowest and the highest values were seen in the group of atrophic brains, while intermediate values were observed both in normal and in edematous brains. There was no correlation with the specific weight.

8. *Water Content of the Central and Convolutional White Matter.*—This varied from 65.7 to 80.06 per cent; the lowest value was obtained in an edematous brain (case 33), and the highest in a moderately atrophic brain (case 29); the next highest value (76.04 per cent), however, was in an edematous brain (case 32). In the majority of cases the values were between 67 and 72 per cent. Although there is no statistical correlation between the water content of the white matter and atrophy or edema, as expressed by the differential ratio, it appears, when the two are plotted together, that relatively high values, above 70 per cent, are found both for atrophic and for edematous brains, while the normal brains, as well as some of the edematous and atrophic brains, show values below 70 per cent. When the water contents of the gray and the white matter are plotted together, not even a trace of correlation is seen (chart 3). This finding is of definite significance and is borne out by the gross and microscopic appearance of pathologic material, especially in cases of cerebral edema. In most cases of edema of the brain (except that produced by occlusion of one of the larger arteries), only the white matter swelled, while the width of the gray cortical ribbon remained normal, or appeared even somewhat narrower in transverse section. There is no correlation of the water content of the white matter and the specific weight of the brain.

In regard to the fact that the water content of the gray matter is consistently greater than that of the white matter, it is of considerable interest to note also that the content of mineral ash of the gray matter is greater than that of the white, as demonstrated by microincineration (Alexander and Myerson [22]). This correlation between water and mineral content can also be demonstrated in embryonic and in tumor tissue, both of which are richer in water, as well as mineral, than normal adult tissue (Scott and Horning [24] and Alexander and Myerson [22]). The inci-

24. Scott, G. H., and Horning, E. S.: Histochemical Studies by Microincineration of Normal and Neoplastic Tissues, Am. J. Path. **8**:329 (May) 1932.

dence of a high water content in atrophic brain tissue may be due to the intensive gliosis in such tissue (Alexander and Looney,[23] figs. 1, 2 and 11), proliferating glial tissue being extremely rich in minerals (Alexander and Myerson [22]) as well as in water.

It is obvious, therefore, from the data given that essential cerebral edema, defined as relative increase in brain volume or decrease in the differential ratio of skull capacity to brain volume, cannot be expressed in simple terms of the water content of either the gray or the white matter. Also, in certain cases of atrophy the water content of the gray and white matter may be increased, but there is reason to believe that this increase in water is offset by an increase in mineral content, especially in the proliferating glial tissue. Cerebral edema, therefore, in

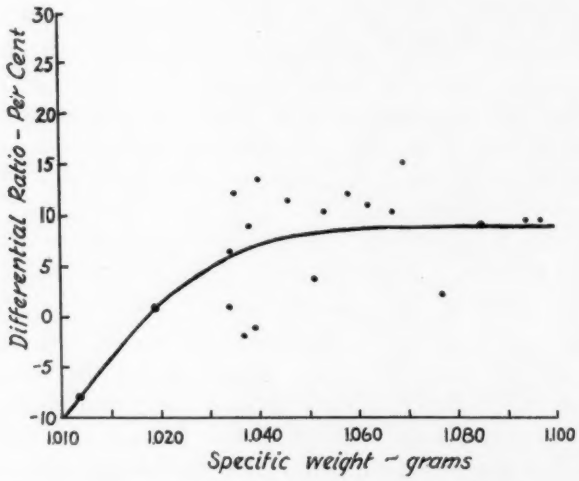


Chart 2.—Specific weights plotted against the differential ratio of skull capacity to brain volume for a series of 20 brains. Note the tendency to a paraboloid curve.

the light of these data, appears to be not so much an absolute increase in water as a shift in its physicochemical association, effecting a change in the water-binding capacity of its colloid and lipoid elements, especially those of the white matter.

9. *Water-Binding Capacity of Brain Tissue.*—It is known that brain tissue and whole brain, if removed from the body, will swell in the medium of a solution at or above the physiologic concentration. In addition to previous work by Hooker and Fischer [25] and Weissberge,[26]

25. Hooker, M. O., and Fischer, M. H.: Ueber die Aufnahme von Wasser durch das Nervengewebe, Ztschr. f. Chem. u. Indust. d. Kolloide **10**:283, 1912.

26. Weissberge, H.: Les variations des poids subies par les tissues musculaires et nerveux dans l'eau et dans quelques solutions salines: Sont-elles conditionnées par des phénomènes osmotiques? Thesis, Paris, 1918.

this has recently been demonstrated by Vandervael [27] for solutions of sodium chloride ranging from 0.9 to 3.6 per cent, Ringer-Locke solution, Tyrode's solution and isotonic (5.5 per cent) solution of dextrose, the p_H of the solutions ranging from 6.85 to 8. Vandervael used dogs, rabbits, guinea pigs, rats and mice, which were killed immediately prior to the experiment by destruction of the medulla oblongata, without previous administration of drugs. Brain tissue when fixed in solution of formaldehyde U. S. P. (1:10) usually does not change its weight or volume

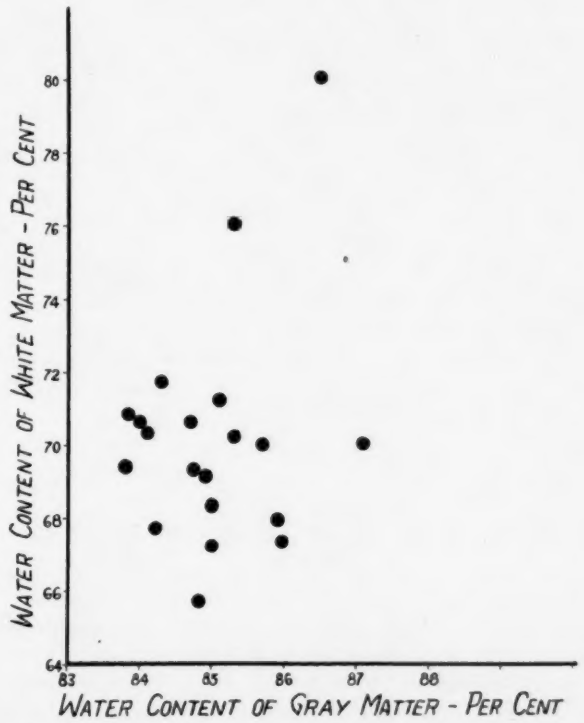


Chart 3.—Water content of gray matter plotted against that of white matter in 20 cases. No apparent correlation is shown.

appreciably during the process of fixation; but one of us (L. A.[1]), when working with material that included a great many cases of extreme dehydration and extreme edema, observed that brain tissue in certain cases shrank and in others swelled during the process of fixation. This postmortem swelling of brain tissue in solutions that did not cause swelling of presumably normal brain tissue was especially remarkable in the

27. Vandervael, F.: Recherches sur l'imbibition du muscle et du cerveau dans les solutions dites physiologiques, Arch. internat. de physiol. **38**:278 (April) 1934.

case of a child aged 6 years, who died of kala-azar, with advanced generalized nutritional anasarca (Alexander,[1] pages 958 and 959).

In our series of cases, brain tissue, when brought into solutions of sodium chloride at concentrations of 1.2, 0.9 and 0.3 per cent or into distilled water, started to swell immediately (chart 4) and continued to do so up to one hundred and ninety hours and more, when the tissue began to show signs of disintegration. The absorption curves for the four solutions did not show appreciable differences in the various cases

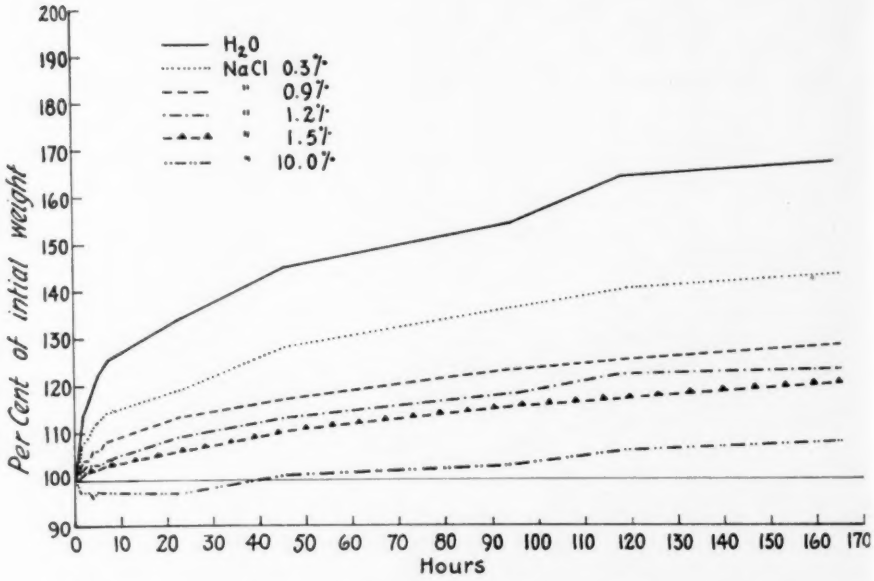


Chart 4.—Absorption curves for tissue from a brain with a normal differential ratio (8.82 per cent) in a woman aged 76 (case 11). The maximum shrinkage in a 10 per cent solution of sodium chloride is 4 per cent, and the preabsorption time, forty hours (presumably a normal curve).

studied (charts 4 to 10). Also, when placed in a 1.5 per cent solution of sodium chloride, the tissue in most of our cases showed immediate swelling, except that in 3 cases of cerebral atrophy (cases 9, 10, 13; charts 5 and 6) and the most severely atrophic areas in a case of Pick's focal atrophy (case 6; chart 10), in which swelling was preceded by slight shrinkage in this solution. The most significant differences in the various cases, however, were shown by the behavior of the tissue in 10 per cent solution of sodium chloride. In all the cases, except in case 16, of cerebral edema (chart 8), the tissue when brought into this solution began to show shrinkage, which lasted for from the first twenty-five to one hundred and ten hours. The lowest point was usually reached within the first six to twenty-four hours. After this time the tissue

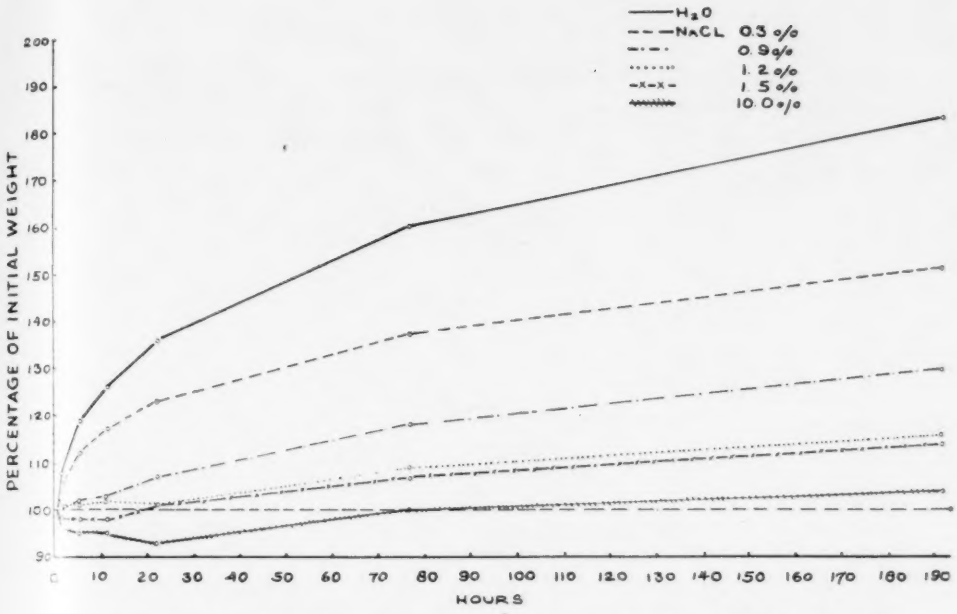


Chart 5.—Absorption curves for tissue from a moderately atrophic (pseudo-atrophic) brain (differential ratio, 9.46 per cent) in a youth aged 19 (case 13), who died of tuberculous enteroperitonitis. The maximum shrinkage in a 10 per cent solution of sodium chloride is 7.1 per cent, and the preabsorption time, seventy-two hours.

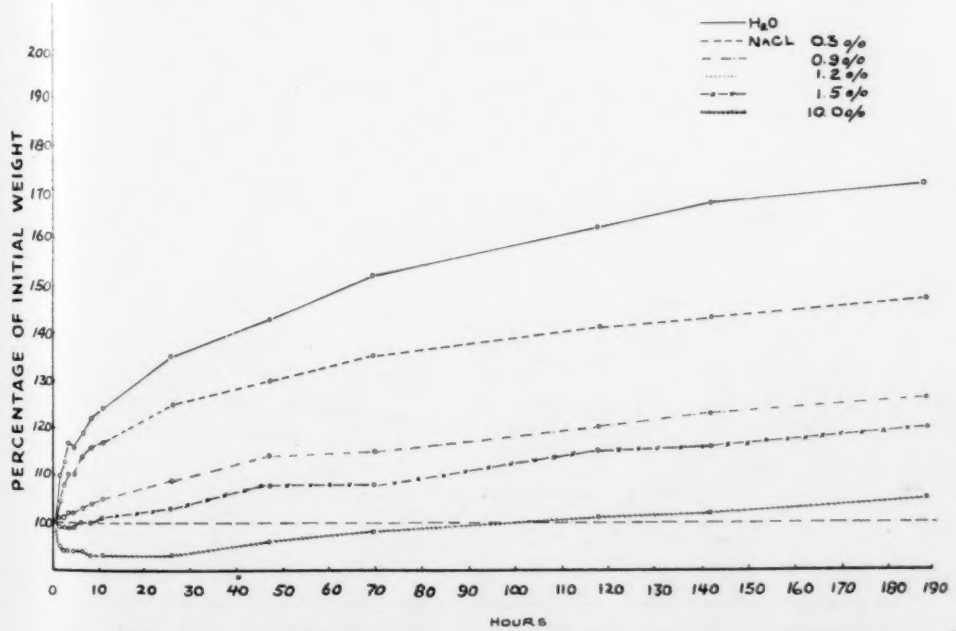


Chart 6.—Absorption curves for tissue from an atrophic brain (differential ratio, 10.96 per cent) in a man aged 65 (case 10). The maximum shrinkage in a 10 per cent solution of sodium chloride is 7.1 per cent, and the preabsorption time, one hundred hours.

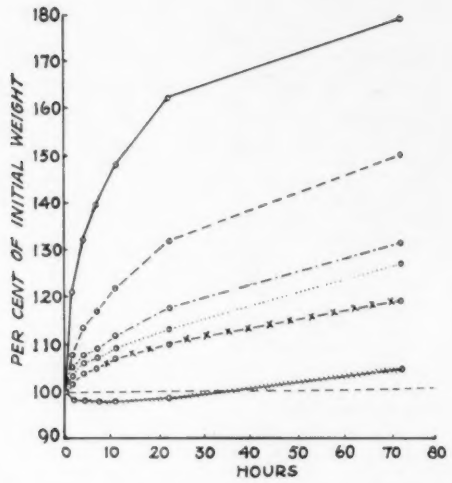


Chart 7.—Absorption curves for tissue from an edematous brain (differential ratio, —7.83 per cent) in a case of nephrosclerosis in a woman aged 40 (case 32). The maximum shrinkage in a 10 per cent solution of sodium chloride is 2.2 per cent, and the preabsorption time, thirty-six hours. In this chart and in charts 8 and 9, the percentages of sodium chloride are indicated by different lines, as explained in chart 6.

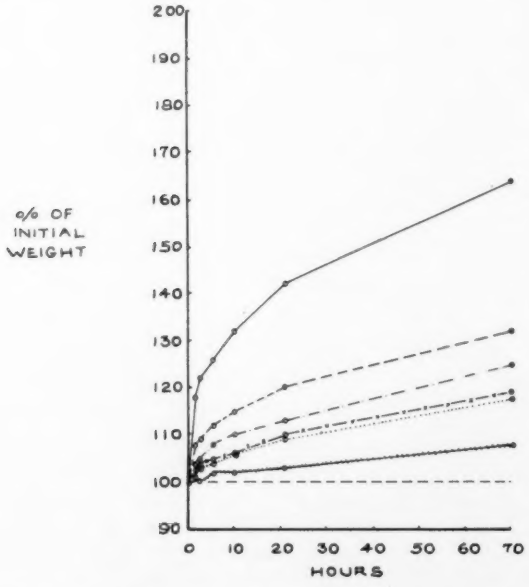


Chart 8.—Absorption curves for tissue from an edematous brain (differential ratio, —1.07 per cent) in a case of poisoning with household lye (commercial potassium hydroxide) in a man aged 29 (case 16). The maximum shrinkage in a 10 per cent solution of sodium chloride and the preabsorption time are reduced to zero.

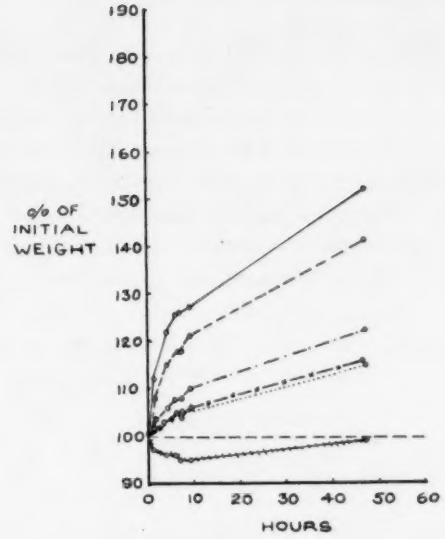


Chart 9.—Absorption curves for tissue from an edematous brain (differential ratio, —1.90 per cent) of a woman aged 36 (case 21) who committed suicide by hanging. The maximum shrinkage in a 10 per cent solution of sodium chloride is 4.5 per cent, and the preabsorption time, fifty-three hours.

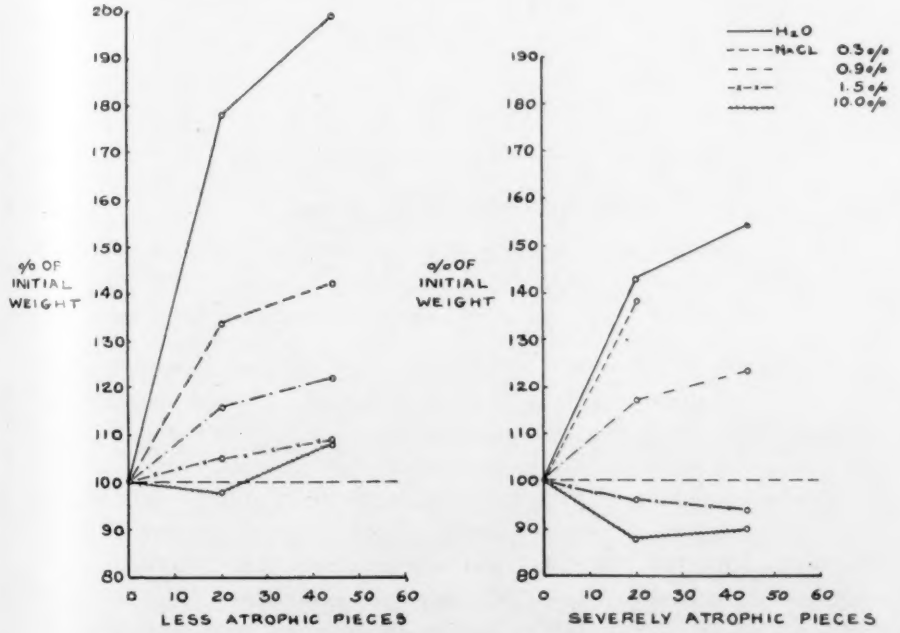


Chart 10.—Absorption curves for tissue in a case of Pick's focal senile atrophy (differential ratio, 29.31 per cent) in a woman aged 72 (case 6). In a 10 per cent solution of sodium chloride, the severely atrophic areas showed greater maximum shrinkage and a longer preabsorption time than the less atrophic areas. The severely atrophic areas shrank and the less atrophic areas swelled in a 1.5 per cent solution of sodium chloride.

started to swell at a slow regular rate. The greatest loss of weight within the initial period of shrinkage in a 10 per cent solution of sodium chloride varied from 2 to 12.4 per cent of the initial weight. In case 16, one of advanced cerebral edema (chart 8), the brain tissue showed no shrinkage at all in a 10 per cent solution of sodium chloride, but started to swell immediately after being brought into this solution. However, in the other cases as well the differences exhibited by the shrinkage-absorption curve in a 10 per cent solution of sodium chloride were sizable and

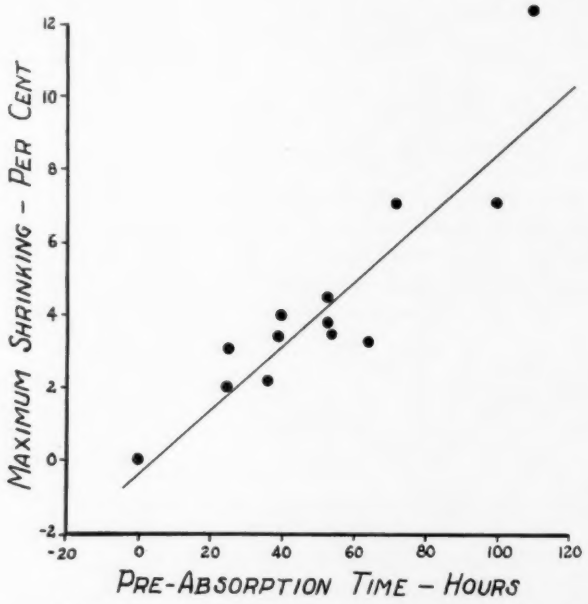


Chart 11.—Maximum shrinkage in a 10 per cent solution of sodium chloride plotted against the preabsorption time in 13 cases. A positive correlation is shown.

clearcut enough to encourage measurement and correlation with other data. Two variables of this curve were measured: (1) the maximum shrinkage of the tissue reached during the period of soaking in the 10 per cent solution of sodium chloride and (2) the "preabsorption time," that is, the time which elapsed until the tissue regained its initial weight in a 10 per cent solution of sodium chloride. These two variables are correlated with each other (chart 11) and can be presented in a straight line equation: Statistically, $r = 0.88$, and the percentage of maximum shrinkage $= -0.6475 + 0.0956$ (preabsorption time); that is, for each ten hours' increase in preabsorption time there was approximately 1 per cent increase in maximum shrinkage. The error of prediction was $\pm$ 1.3 per cent.

The maximum shrinkage varied from 0 to 12.4 per cent. If one correlates these values with the differential ratio (of skull capacity to brain volume), one finds (chart 12) that, while there is not sufficient correlation to compute a coefficient, all the brains which were characterized as edematous by their differential ratios showed a maximum shrinkage value below 5 per cent, while all the brains with maximum shrinkage levels above 6 per cent were atrophic. The only values above 7 per cent were observed in 4 cases of cerebral atrophy. The brains with a normal differential ratio showed a maximum shrinkage of from 3 to 4 per cent. The average maximum shrinkage for atrophic brains (7 cases) was 6.3 per cent; that for edematous brains (5 cases), 2.9 per cent, and

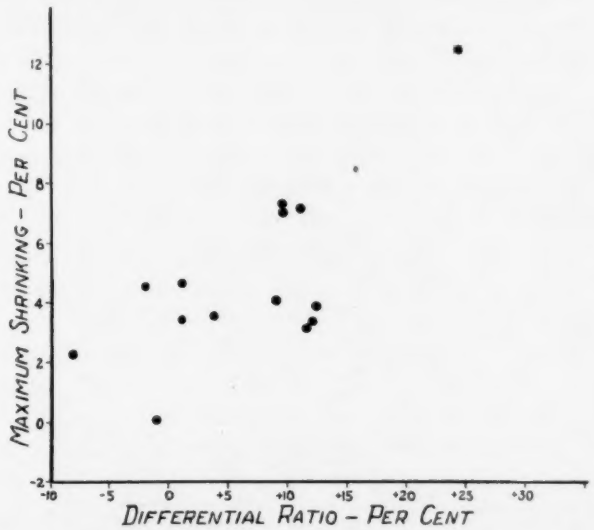


Chart 12.—Differential ratio of the skull capacity to the brain volume plotted against the maximum shrinkage in a 10 per cent solution of sodium chloride in 14 cases. The values tend to increase together.

that for brains with normal differential ratio, 3.75 per cent. Although the highest values (above 7 per cent) were observed in cases of atrophy and the lowest values in cases of edema of the brain, the intermediate values did not show any significant trend. One must conclude that although there is, undoubtedly, a relation between these factors, it is subject, apart from the extreme values, to a great deal of variation (balancing factors).

If the maximum shrinkage is plotted against the specific weight, a definite tendency appears for the maximum shrinkage to be higher in brains with high specific weights (that is, atrophic brains) and lower in brains with intermediate and low values. The trend, however, is too weak to be considered significant. There is no correlation of the maxi-

mum shrinkage with the water content of either the gray or the white matter.

The "preabsorption time" varied from zero to one hundred and ten hours. When the preabsorption time is plotted against the differential ratio of skull capacity to brain volume (chart 13), one finds that all edematous brains in our group showed values below fifty-five hours, while all brains with a preabsorption time above sixty hours were atrophic. The brains with a normal differential ratio showed preabsorption times between forty and sixty hours. The average preabsorption time for the atrophic brains was seventy-six hours, for the edematous brains thirty-two hours and for the normal brains forty-seven hours. Here, too, the intermediate values did not show a significant trend. We feel justified in concluding that there is a definite positive relation, with, however, many exceptions.

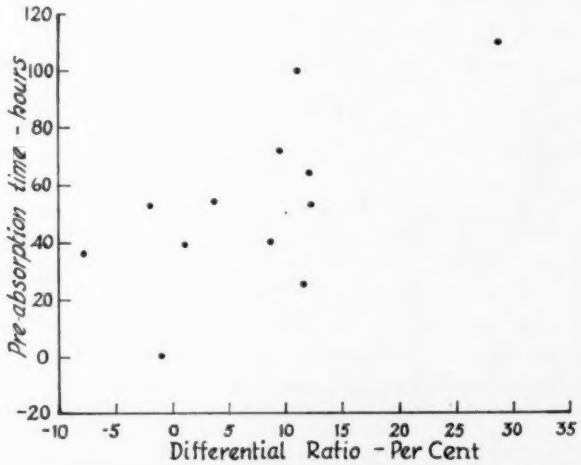


Chart 13.—Differential ratio of the skull capacity to the brain volume plotted against the preabsorption time in a 10 per cent solution of sodium chloride in 12 cases. Some general correlation is shown.

There was an insignificant trend in the relation of preabsorption time and specific weight, similar to that of maximum shrinkage and specific weight. There was no correlation of the preabsorption time and the water content of either the gray or the white matter.

Charts 4 to 10 show illustrative absorption curves for brain tissue in distilled water and solutions of sodium chloride of from 0.3 to 10 per cent. Chart 4 shows the absorption curves for the tissue from a brain with normal differential ratio (8.82 per cent). The maximum shrinkage in a 10 per cent solution of sodium chloride was 4 per cent, and the preabsorption time, forty hours. Chart 5 shows the absorption curves for a moderately atrophic brain (differential ratio, 9.46 per cent). The

maximum shrinkage was 7.1 and the preabsorption time seventy-two hours. Chart 6 shows the absorption curves for tissue from an atrophic brain (differential ratio 10.96 per cent). The maximum shrinkage in a 10 per cent solution of sodium chloride was 7.1 per cent, and the preabsorption time, one hundred hours.

Chart 7 shows the absorption curves for the tissue from an edematous brain (differential ratio, —7.83 per cent) in a case of nephrosclerosis. The maximum shrinkage in a 10 per cent solution of sodium chloride was 2.2 per cent, and the preabsorption time, thirty-six hours. Chart 8 shows the absorption curves for the tissue from another edematous brain (differential ratio, —1.07 per cent) in a case of poisoning with household lye (commercial potassium hydroxide). In this case, the maximum shrinkage in a 10 per cent solution of sodium chloride and the preabsorption time were reduced to zero, since the tissue started to swell immediately when brought into a 10 per cent solution of sodium chloride. In both these cases, in the second more than in the first, there was a definite increase in the postmortem water-binding capacity of the tissue in a 10 per cent solution of sodium chloride. Chart 9 shows the absorption curves for the tissue from an edematous brain (differential ratio, —1.9) in a case of suicide by hanging. In this case there was neither increase nor decrease in the postmortem water-binding capacity of the brain tissue; the maximum shrinkage in a 10 per cent solution of sodium chloride was 4.5 per cent, and the preabsorption time, fifty-three hours. Chart 10 shows absorption curves for severely diseased and for grossly approximately normal, histologically less severely involved tissue in a case of Pick's focal senile atrophy (differential ratio, 29.31 per cent). The less atrophic areas showed approximately normal absorption curves (coming close to some of those seen for edematous brains), namely, a maximum shrinkage of 2 per cent and a preabsorption time of twenty-five hours. The severely atrophic areas showed a maximum shrinkage of 12.4 per cent and a preabsorption time of one hundred and ten hours; in addition, the tissue also shrank in a 1.5 per cent solution of sodium chloride, while the tissue from the less atrophic areas showed swelling in a solution of sodium chloride of this concentration. Comparison of the two curves shows that in a case of Pick's focal senile atrophy the postmortem water-binding capacity in 10 and 1.5 per cent solutions of sodium chloride of tissue from atrophic cortical areas is diminished as compared with that of tissue from the grossly normal, histologically less severely atrophic areas of the same brain.

The question arises whether or not these absorption curves represent true biologic phenomena. In order to inquire into this matter, we have subjected them to further analysis. If one constructs the curves for the various times at which readings were taken after the blocks of tissue had been brought into the various test solutions and plots the

percentages of sodium chloride in the solutions on the x axis and the percentages of the initial weight of the tissue blocks on the y axis, one can determine the percentages of sodium chloride in solution at which the time curves cross the 100 per cent axis (chart 14). These points determine the percentages of sodium chloride which are necessary to obtain no change in volume at the various times presented in the curves. These are, in case 11, for instance, 1.9 at two hours, 2.1 at seven hours, and 3.1 at twenty-three hours. If one plots these "percentages of sodium chlo-

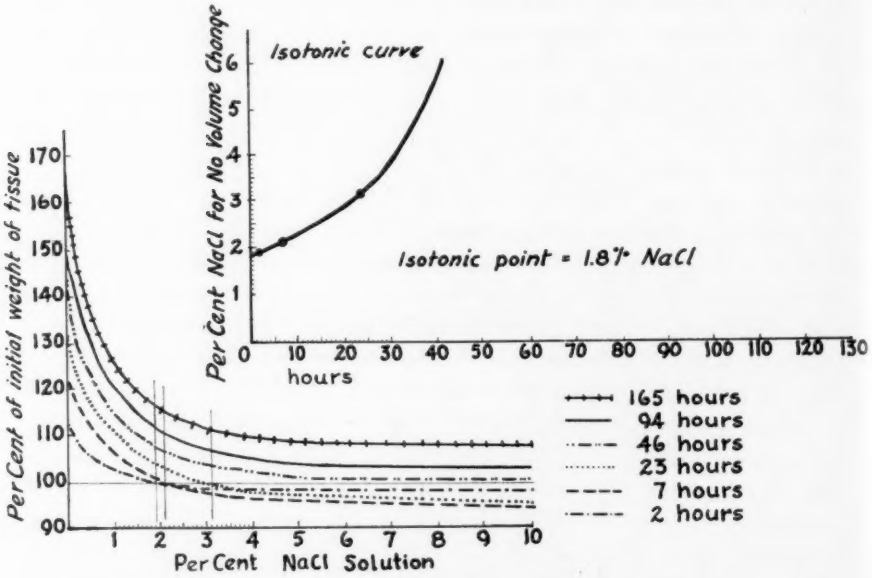


Chart 14.—A presumably normal isotonic curve for tissue from a brain with normal differential ratio and the derivation of the curve (case 11). The curve in the lower left corner shows the time curves, by means of which the isotonic curve is derived from the original absorption curves given in chart 4. Instead of plotting the time against the percentage of the initial weight for the various concentrations of sodium chloride, as in chart 4, the percentages of sodium chloride are plotted against the percentages of the initial weight for the various periods of time at which readings were taken. The point at which any of these time curves crosses the axis representing 100 per cent of the initial weight determines the percentage of sodium chloride at which no change in weight or volume occurred at that time. These percentages (indicated by vertical lines drawn through the points of crossing) are: 1.9, at two hours; 2.1, at seven hours, and 3.1, at twenty-three hours. If the percentages of sodium chloride in solution in which tissue showed no change in weight or volume at a given time are plotted on the ordinates and the times on the abscissas, the isotonic curve can be drawn (curve in the upper right corner). By exterpolating from the time of first measurement to zero hours, the postmortem isotonic point for the normal brain tissue in this case can be assumed to be equivalent to a 1.8 per cent solution of sodium chloride.

ride required for no change in volume" on the y axis and the time, expressed in hours, on the x axis, one can draw the isotonic curve of the tissue; by exterpolating from the time of the first measurement to zero hours, one may be allowed to conjecture as to the isotonic point of the tissue (chart 14). In case 11, in which the differential ratio of skull capacity to brain volume was normal, and in case 31, in which there was a slightly decreased differential ratio, which could, however, still be regarded as low normal, the isotonic point, as calculated by this method, was 1.8 per cent (chart 14, illustrating case 11). For atrophic brains, with decreased water-binding capacity of the tissue, this point was lower, namely, 1.1 per cent (chart 15, illustrating case 10). For edematous brains with increased postmortem water-binding capacity of the tissue, this point was higher; in case 16 it was above 10 per cent (chart 16).

It must be concluded, therefore, that the isotonic points, as determined from these curves, cannot be those prevailing during life, since the isotonic points for serum and for spinal fluid, calculated from determination of the freezing point by Fremont-Smith and his co-workers [28] are equivalent to 0.891 and 0.886 per cent of sodium chloride, respectively. This indicates, therefore, that at the time of death a profound alteration of the osmotic relation of the tissue is taking place, since not only human autopsy material but brain tissue from experimental animals, removed immediately after killing the animal, shows this deviation of the isotonic point. This fact, however, does not detract from the value which the determination of the postmortem isotonic point of the tissue may have for purposes of comparison, since in human autopsy material, *ceteris paribus,* differences in the postmortem isotonic point are observed which are positively related to different pathologic conditions, such as atrophy or edema of the brain.

If one plots the isotonic curve for grossly normal brain tissue (case 11) and that for atrophic brain tissue (case 10) on the same scale (chart 17), one finds that the normal tissue behaves in an almost linear fashion, whereas the atrophic tissue, starting at a lower level, begins in the same fashion within the first four hours but accelerates gradually, as expressed in the equation [29] $y = x^2 \pm c$, in contrast to the function

28. Fremont-Smith, F.; Dailey, M. E.; Merritt, H. H.; Carroll, M. P., and Thomas, C. W.: The Equilibrium Between Cerebrospinal Fluid and Blood Plasma: I. The Composition of the Human Cerebrospinal Fluid and Blood Plasma, Arch. Neurol. & Psychiat. **25**:1271 (June) 1931. Fremont-Smith, F.; Thomas, G. W.; Dailey, M. E., and Carroll, M. P.: The Equilibrium Between Cerebrospinal Fluid and Blood-Plasma: V. The Osmotic Pressure (Freezing-Point Depression) of Human Cerebrospinal Fluid and Blood Serum, Brain **54**:303 (Sept.) 1931.

29. Dr. Michel Pijoan, of the Harvard Medical School and the Peter Bent Brigham Hospital, made the calculations in these equations.

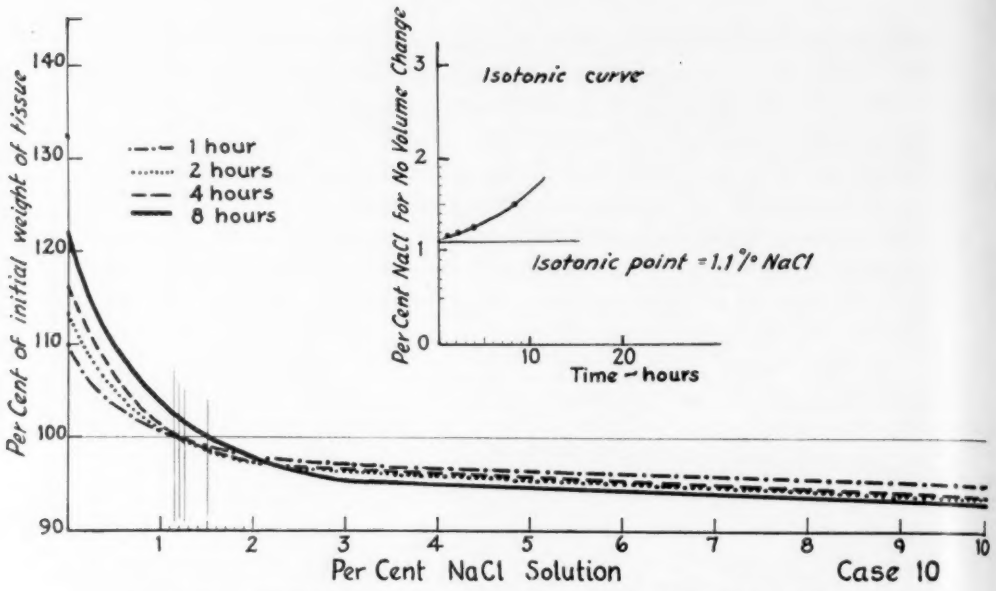


Chart 15.—Isotonic curve for tissue from an atrophic brain (case 10) and the derivation of this curve (compare with charts 6 and 14).

The percentages of sodium chloride at which no change in weight or volume of the tissue occurred are: 1.15, at one hour; 1.2, at two hours; 1.25, at four hours, and 1.5 at eight hours. Correspondingly, the postmortem isotonic point for the atrophic brain tissue in this case is lower than that for normal brain tissue (compare with chart 14); it is equivalent to a 1.1 per cent solution of sodium chloride.

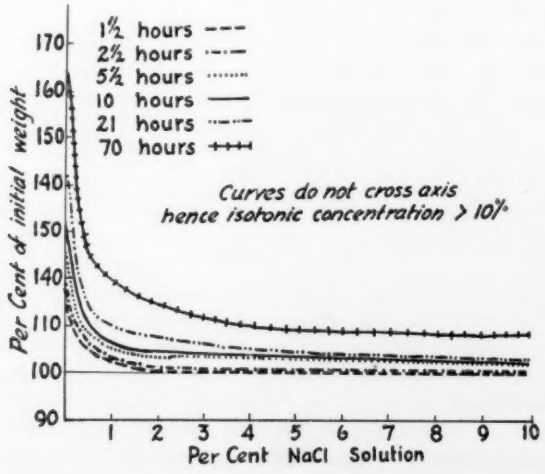


Chart 16.—Curves for determination of the isotonic point for tissue from an edematous brain (case 16). They may be compared with chart 8. No isotonic curve can be constructed with the percentages of sodium chloride employed.

of the activity of the normal tissue, as expressed in the equation $y = \frac{1}{2} x \pm 1.8$.

The relationship of the two acting differently, but constantly, in this capacity is $y = \frac{1}{32} x^2 + \frac{1}{2} x + 1.8$.

These differences may be related to differences in the physicochemical state of the organic compounds of the myelin of the white matter, which always show early alteration in edema of the brain, or to a difference in the amount and distribution of tissue minerals. In cerebral edema, sodium increases to 1.4 times the normal value in the gray matter and to 2.5 times the normal value in the white matter; calcium, to 1.8 times the normal value in the gray matter and to 3.6 times the normal value in the white matter; iron increases to 1.8 times

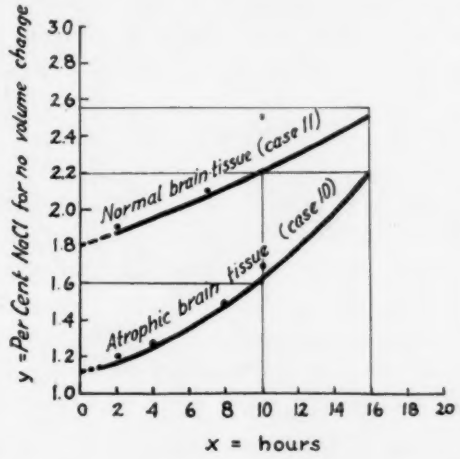


Chart 17.—The isotonic curves for tissue from normal and atrophic brains, plotted on the same scale (compare charts 4, 6, 14 and 15). The curve for normal brain tissue behaves in almost linear fashion, and that for atrophic tissue starts similarly, though from a lower level, but after four hours accelerates gradually, according to the equation given in the text.

the normal value in the gray matter, while it remains unaltered in the white matter. These findings were made by spectroscopic examination (Alexander and Myerson) [30] in a case of unilateral cerebral edema due to abscess of the brain on the same side, the unaltered hemisphere serving as the normal control. This increase in tissue minerals may well explain in part the comparatively high postmortem isotonic points and the increased postmortem water-binding capacity of edematous

30. Alexander, L., and Myerson, A.: Minerals in Normal and in Pathologic Brain Tissue, Studied by Micro-Incineration and Spectroscopy, Arch. Neurol. & Psychiat. **39**:131 (Jan.) 1938.

brains. This is probably also the explanation of a recent finding by Schlüter and Seifert,[31] who demonstrated lowering of the freezing point of the white matter of edematous brains. On the other hand, areas of cortical atrophy are depleted of minerals (Alexander and Myerson);[22] this may in part explain the comparatively low postmortem isotonic points and the decreased postmortem water-binding capacity of tissue from atrophic brains and from circumscribed areas of cortical atrophy.

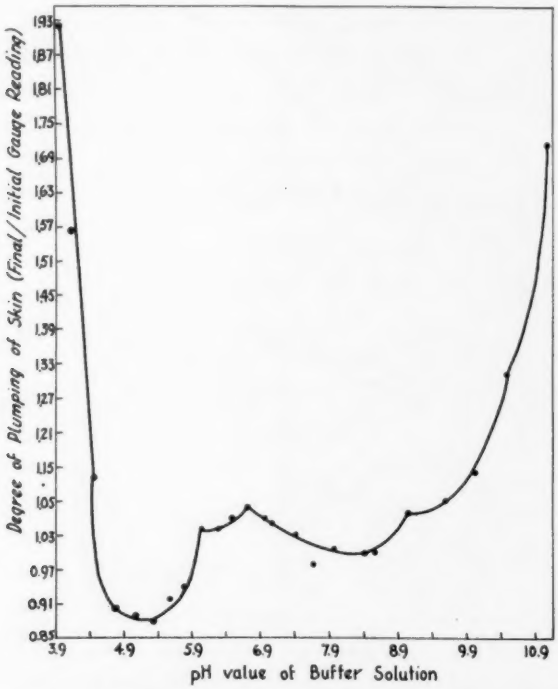


Chart 18.—Swelling ("plumping") of skin in solutions of different p_H, such as are used in the leather industry (by permission of Miss E. Heath). An explanation is given in the text.

10. *p_H of Brain Tissue.*—The postmortem p_H of brain tissue varied from 5.81 to 7.19; that in the majority of the cases of our group was between 6.4 and 6.7. Although the highest of the p_H values in our cases, and the only one above 7, was observed in case 16, that of advanced cerebral edema in a person who committed suicide by drinking household lye (commercial potassium hydroxide), no consistent correlation was seen between the value for p_H and edema or atrophy, as expressed by the differential ratio of skull capacity and brain volume.

31. Schlüter and Seifert, cited by Terplan, K. L.: Histopathological Changes in Marked Swelling of the Brain, Am. J. Path. **13**:664 (July) 1937.

This observation parallels the experience recorded by the leather industry for the postmortem swelling ("plumping") of skin, which shows that at the range of p_H values for our samples (from 5.81 to 7.19) no marked changes in volume take place while intensive swelling occurs at p_H values below 4.9 and above 9.9 (chart 18; by permission of Miss E. Heath).

There is also no correlation of the p_H and the water content of the gray or the white matter or of the p_H and the maximum shrinkage and preabsorption time.

The p_H values for human brain tissue post mortem are definitely not related to those prevailing during life, but probably are correlated with postmortem glycolysis. Holmes [32] found that the p_H of brain tissue of experimental animals, measured immediately after killing, was low (acid) in normal and hyperglycemic animals and fell in correlation with the postmortem decrease in sugar content and the increase in lactic acid, while it was high (alkaline) in hypoglycemic animals and fell only slowly.

SUMMARY

1. Atrophy or edema of the brain can be measured quantitatively only by the differential ratio of skull capacity to brain volume or brain weight. The weight of the brain or its volume alone does not measure, or even sufficiently indicate, atrophy or edema.

2. The differential ratio of skull capacity to brain volume is the difference between these two variables, expressed as the percentage of skull capacity. The normal range varies from 4 to 9 per cent. A ratio below 4 per cent expresses edema; one above 9 per cent atrophy.

3. The water content of the gray matter is significantly and constantly higher than that of the white matter. The "normal" range of values is from 84 to 86 per cent for the gray matter and from 67 to 72 per cent for the white matter; the total range of variations for the gray matter is from 83 to 87 per cent, and that for the white matter, from 66 to 80 per cent. The higher water content of gray matter is associated with a higher content in ash, especially electrolytes (Alexander and Myerson.) [33]

4. The water content of the white matter shows no positive correlation with that of the gray matter, nor is either positively correlated with edema or atrophy of the brain. Therefore, edema of the brain cannot be expressed in terms of increase, nor atrophy as decrease, in the total water content.

---

32. Holmes, E. G.: Observations on the Variation of p_H of Brain Tissue, Biochem. J. **26**:2010, 1932.

33. Alexander and Myerson (footnotes 22 and 30).

5. The postmortem water-binding capacity of tissue from edematous brains is increased; that of tissue from atrophic brains and from localized areas of cortical atrophy is decreased. Correspondingly, the postmortem isotonic point is higher for edematous brain tissue and lower for atrophic brain tissue.

6. Atrophy or edema of the brain is not associated with a significant shift in postmortem p_H, the latter possibly being related to postmortem glycolysis.

MENTALITY OF DISPENSARY EPILEPTIC PATIENTS

MARGARET R. BARNES, PH.D.
AND
JOSEPH L. FETTERMAN, M.D.
CLEVELAND

In an earlier paper we [1] reported the results of a serial study of the intelligence of 105 patients at the epileptic clinic of the Lakeside Hospital Dispensary. We found at the initial examination that the average intelligence quotient for the entire group was 74, with a range of from 35 to 130. (The majority of those who were retested at a later date did not show a decline in the intelligence quotient.)

To date, 35 of these patients have been tested, each from three to eight times, at intervals of a year or more, with the Stanford revision of the Binet test for general intelligence. Table 1 shows the results of these tests and includes data on the type of epilepsy, the duration of the attacks, expressed in years, the initial intelligence quotient and the fluctuation of the quotient from test to test.

S. S. (case 32), whose condition was diagnosed as idiopathic epilepsy, had been subject to spells for thirteen years when first tested, ten years ago. The initial intelligence quotient was 91; at the second test he had gained about 14 points. In subsequent tests, he lost 9 points, then gained 12, then lost 20 and a year later regained the loss. Apparently, he had fluctuations which were dependent, among other factors, on the proximity to or freedom from attacks. But the significant observation in his case is the fact that a patient with frequent seizures, which extended over twenty-three years, showed when last tested an intelligence quotient even higher than that found at the initial examination, a decade before. In checking the loss of 20 points, we found that the test had come shortly after a series of convulsions and that the subsequent gain was made after a period of apparent well-being.

The group as a whole showed fluctuations from test to test, but on the average the losses were offset by gains of almost equal amount. Indeed, there was a small, but insignificant, excess of gains. It is of interest to find that only 1 of the 35 patients who were retested showed steady losses. This patient had been checked three times in a period of several years, and the losses were small: 6 points from the first to the second test and 1 point from the second to the third test. Five patients, on the other hand, showed consistent gains from year to year.

---

1. Fetterman, J. L., and Barnes, M. R.: Serial Studies of the Intelligence of Patients with Epilepsy, Arch. Neurol. & Psychiat. **32**:797 (Oct.) 1934.

From this serial study we concluded that mental deterioration, as measured by a decrease in the Binet intelligence quotient, does not take place in all patients to the degree reported by some authors, such as Dawson and Conn,[2] who recorded a uniform decrease in the intelligence quotient in epileptic children from the first to the second test. Our results support Paskind's [3] conclusions, drawn from a large group of

TABLE 1.—*Changes in the Binet Intelligence Quotient in Three or More Tests* *

Case No.	Patient	Type of Epilepsy	Duration of Epilepsy, Yr.	Initial Intelligence Quotient	Change in Intelligence Quotients in Tests After						
					1-2 Yr.	2-3 Yr.	3-4 Yr.	4-5 Yr.	5-6 Yr.	6-7 Yr.	7-8 Yr.
1	R. G.	Idiopathic	30	72	— 6	— 1	....	....	....	....	....
2	B. K.	Alcoholic	5	71	— 3	+ 7	....	....	....	....	....
3	J. M.	Idiopathic	10	95	+ 5	—21	....	....	....	....	....
4	H. O.	Idiopathic	3	71	— 7	+11	....	....	....	....	....
5	G. T.	Idiopathic	13	69	0	+13	....	....	....	....	....
6	S. Sh.	Birth trauma	10	69	+ 5	0	....	....	....	....	....
7	L. K.	Idiopathic	14	81	+13	— 1	....	....	....	....	....
8	R. B.	Idiopathic	3	101	+ 6	— 2	....	....	....	....	....
9	G. B.	Glandular	15	91	+ 5	—14	....	....	....	....	....
10	H. S.	Hysterical	10	47	+ 7	— 4	....	....	....	....	....
11	E. G.	Postencephalitic	18	61	+ 9	+17	....	....	....	....	....
12	G. W.	Idiopathic	9	44	+ 3	+10	....	....	....	....	....
13	E. J.	Idiopathic	8	79	— 4	+17	....	....	....	....	....
14	M. R.	Organic	7	69	+11	— 2	....	....	....	....	....
15	P. M.	Idiopathic	44	57	+ 5	+ 4	....	....	....	....	....
16	W. Mc.	Idiopathic	17	62	+ 2	0	— 4	....	....	....	....
17	S. B.	Idiopathic	24	99	+ 8	— 6	+ 8	....	....	....	....
18	B. B.	Organic	10	81	—14	— 8	+ 1	....	....	....	....
19	L. B.	Idiopathic	7	88	+ 5	— 5	—14	....	....	....	....
20	M. K.	Idiopathic	24	75	+ 6	— 4	+ 5	....	....	....	....
21	L. S.	Idiopathic	13	85	— 2	— 2	+ 5	....	....	....	....
22	A. C.	Idiopathic	31	84	— 7	+10	— 1	....	....	....	....
23	R. S.	Idiopathic	5	64	— 5	+ 5	+ 1	....	....	....	....
24	M. D.	Organic	7	58	+ 2	— 3	— 3	....	....	....	....
25	L. B.	Organic	7	88	+ 6	— 4	+12	— 1	....	....	....
26	M. G.	Idiopathic	15	85	+ 8	— 6	+ 6	+ 6	....	....	....
27	R. H.	Organic	2	66	— 3	+ 5	— 7	+ 7	....	....	....
28	E. K.	Idiopathic	14	63	— 1	+ 9	— 4	— 4	....	....	....
29	L. D.	Idiopathic	15	59	+ 2	+ 4	— 2	— 3	....	....	....
30	S. B.	Idiopathic	12	64	— 5	+14	— 4	+ 1	....	....	....
31	E. H.	Idiopathic	28	64	— 2	— 2	— 3	+12	— 3	....	....
32	S. S.	Idiopathic	13	91	+14	— 9	+12	—20	+18	....	....
33	M. H.	Idiopathic	5	87	—17	+ 1	+24	— 8	— 2	— 8	....
34	M. S.	Idiopathic	19	68	— 2	—15	+14	— 4	+ 2	— 2	+ 5
35	V. V.	Idiopathic	8	73	+ 3	+ 2	— 1	— 2	+ 7	— 4	+ 1

* This table gives the initial intelligence quotient and the subsequent changes from test to test. The retests were made at an interval of from one to two years; thus, all the patients who have had four or more tests have been followed for from five to ten years.
In this table, — indicates a loss and + a gain in the intelligence quotient.

private patients, that if the ability to continue at one's work is an index of the amount of deterioration, only 6 per cent of epileptic patients are deteriorated. Paskind asserted, therefore, that 94 per cent of his patients did not show significant deterioration.

2. Dawson, S., and Conn, J. C. M.: The Intelligence of Epileptic Children, Arch. Dis. Childhood **4**:142 (June) 1929.

3. Paskind, H. A.: Extramural Patients with Epilepsy, with Special Reference to Frequent Absence of Deterioration, Arch. Neurol. & Psychiat. **28**:370 (Aug.) 1932.

Our lack of evidence of deterioration with the Binet test leads to the consideration of three possibilities, which should be checked: (1) that the patients may have deteriorated mentally at some time in the past and have reached a plateau, or constant level, before we began to study them; (2) that deterioration in some cases was so slow as not to be detected in the ten year period, and (3) that we used a test instrument inappropriate to our needs.

METHOD

The Binet test is obviously of no use in attacking the first problem because it gives only the patient's present reaction to the test as a whole and does not indicate his former mental level. Thus, one is unable to distinguish by this test between the originally dull person and a person who was formerly of a higher mental status but has deteriorated to a lower level.

The Babcock Test.—A different approach may be made to this subject by taking as a basis the clinical manifestations of the mentality of the deteriorated person. Here one finds, except in the worst forms, relatively unimpaired old learning, but definite slowness of response and inability to fix new impressions. If one can find a means to measure quantitatively these qualitative differences, one will have a test instrument adapted to one's needs. The most accessible and reliable index of a patient's old learning is his vocabulary. "Words when once learned are not quickly forgotten and remain as indications of the ability a person once had, since some kinds of words cannot be learned by persons of inferior intelligence and the type of word one can learn is highly correlated with intelligence, as measured by the criterion of ability in school and college work" (Babcock [4]).

In contrast to this old learning, one would have a measure of the patient's mode of reaction to new impressions, particularly the speed of response, thus measuring the efficiency with which he uses his mentality.

In 1930 Dr. Babcock published a test based on exactly these considerations; [4] we began to use this test in 1931. Dr. Babcock employed as a criterion of the subject's former mental level his rating on the Terman vocabulary test.[5] This test correlates highly with the intellectual level and is dependent on previously formed associations. The efficiency aspect of the patient's intelligence is next determined by means of twenty tests which depend on new learning and speed of response. (The reader is referred to Dr. Babcock's papers for details of the theory, technic and results of these tests.)

The scores for the vocabulary test give a rating of the patient's former mental level, and the average of the scores on the twenty tests, emphasizing the efficiency aspect, is called the patient's efficiency score. The discrepancy between the two scores is a measure of the relation which the subject's present efficiency bears to his former intellectual level and is known as the subject's efficiency index. Norms for this test were established for a group of normal adults, and its validity as a measure of deterioration has been established by work done by Dr. Babcock [6] on

4. Babcock, H.: An Experiment in the Measurement of Mental Deterioration, Arch. Psychol., 1930, no. 117.

5. Terman, L. M., and others: Genetic Studies of Genius, Stanford University, Stanford University Press, 1925, vol. 1.

6. Babcock, H.: Dementia Praecox: A Psychological Study, Lancaster, Pa., Science Press Printing Company, 1933.

patients with dementia paralytica and schizophrenia. Her results were confirmed by Gilbert,[7] in a study of senescence, and by Schwartz [8] and Wittman,[9] in independent studies of schizophrenia.

This work has established that the discrepancy between the former mental level and the present efficiency score must be one of at least three and one-half years to represent a pathologic loss. This means that an efficiency index of —3.5 years or lower is significant of pathologic deterioration.

We have given the Babcock test to 54 epileptic patients, 33 of whom have been tested two or more times. The results are summarized in table 2. We found among the epileptic patients a wider range of efficiency indexes than did Dr. Babcock in her normal group, but we found no patient scoring as low as in the dementia paralytica group. Only 5 patients, or 11 per cent, had efficiency indexes of —3.5 years.

We recognize that we have been working with a selected group of patients, for the obviously deteriorated patients are sifted and sent to institutions. As for

TABLE 2.—*Range of Efficiency Indexes Obtained with the Babcock Test* *

Condition	No. of Patients	Lowest Individual Score	Median Score	Highest Individual Score
†Normal	228	— 3.0	+0.10	+3.2
†Schizophrenia		—13.1	—3.50	+0.5
†Dementia paralytica		— 9.2	—4.80	—0.6
Improving		— 9.0	—4.05	—0.6
Not improving		— 9.2	—5.30	—1.50
Epilepsy		— 5.0	—0.81	+5.0

* This table compares our figures with those for normal and deteriorated patients reported on by Miss Babcock. The average loss for our group of patients, though somewhat above that for the normal group, is strikingly less than that for the groups with schizophrenia and dementia paralytica.

In this table, + indicates efficiency levels above average, and —, those below average. The efficiency indexes are expressed in terms of years.

† Results of Babcock's studies (footnotes 4 and 6).

any difference which may exist between the mentality of the normal person and the patient with epilepsy: We found that our patients had lost about one year in efficiency. This amount, though slight, is statistically significant.

RELATION OF NUMBER OF SEIZURES TO EFFICIENCY INDEX IN THE BABCOCK TEST

We analyzed our data to determine the influence of three factors which might be involved: the age, the number of attacks to which a patient has been subjected and the total duration of illness. (A statistical treatment of this material is the subject of another paper in preparation by one of us [M. R. B.] for a journal of psychology.) The average chronologic age for our group of patients was 27.33 years, and the range, from 15 to 52. Since increasing age is known to be a factor in mental deterioration, account must be taken of the chronologic age.

7. Gilbert, J.: Mental Efficiency in Senescence, Arch. Psychol., 1935, no. 188.

8. Schwartz, R.: Mental Deterioration in Dementia Praecox, Am. J. Psychiat. **12**:555, 1932.

9. Wittman, P.: Unpublished data; cited by Babcock.[6]

The relative importance of the number of attacks and the duration of the disease processes was studied. By means of a partial correlation technic, we found that chronologic age is not a significant factor in accounting for the difference between the epileptic patients in our series and normal persons. The group was apparently sufficiently homogeneous, and on the average the patients were too young to be suffering from the effects of increasing age.

Likewise, the number of attacks, as such, does not account for the difference. We subdivided the 54 patients into two groups, those having few and those having frequent attacks. We found that the patients suffering from infrequent seizures showed the same slight loss as those who suffered from frequent attacks.

When the duration of time in which the patient had been subject to attacks was examined, chronologic age and the number of attacks being kept constant, it was determined that duration of the disease is a significant factor in the loss of efficiency of the epileptic patient.

Lennox [10] stated that the total number of spells a patient has is a determining factor in deterioration. This observation tallies with our findings, for usually the patient who had the greatest number of attacks was also subject to them the longest. Analysis of our data is a statistical verification of the recent clinical concept that the attack per se is not the all-important factor in producing deterioration. The attack is only a symptom of the underlying process, which may also produce deterioration.

COMMENT

The clinical experience of Paskind, the report of Lennox and our own psychologic measurements show that certain persons may suffer from a convulsive disorder for years without serious impairment of intelligence. The Babcock test showed a slight loss of efficiency in many epileptic patients, especially those who had had the illness for many years.

How is one to explain the more serious instances of major mental change associated with epilepsy? Several possible explanations suggest themselves: (1) the damaging influence of convulsions; (2) the dulling effect of medication; (3) the restrictions imposed by the attacks; (4) the social and psychologic discomforts resulting from seizures, and (5) the inherent cerebral defect.

The Attack.—The psychic upheaval of each attack, with its threatening warning or sudden seizure, the period of unconsciousness and the confusion and stupor which follow represent a serious, even if temporary, cerebral disturbance. Grossmann [11] described this experi-

10. Lennox, W. G.: Epilepsy, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1933, vol. 6, p. 628.

11. Grossmann, I.: Theorie des epileptischen Charakters, Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:12, 1928.

ence as "an anxiety of death reexperienced with each convulsion." Also, on the physiologic side tissue damage may result from the anoxemia associated with cyanosis, the venous congestion and the possible cranial trauma from a fall.

Theoretically, such processes occurring repeatedly may lead to intellectual loss, and possibly this accounts for the deterioration of certain epileptic patients.

Nevertheless, our results tend to relieve the attacks of major responsibility. Many of our patients, studied over a period of years, do not show deterioration. Likewise, comparison of a group of patients suffering from many attacks and those subject to few attacks showed no appreciable difference with the Babcock test. Lennox mentioned a case in which the patient had had thousands of attacks during a span of years and yet retained superior intelligence. Dostoevski's "The Brothers Karamazov," published at 60, was as brilliant as his "Poor People," written at 24, though a lifetime of epileptic seizures intervened.

Medication.—The large doses of sedatives necessary in the treatment of epilepsy may exert a deleterious effect. This may operate particularly in patients who are sensitive to bromides or to barbital. Toxic psychoses are known to develop from such medication. From a practical standpoint, however, we do not recall any cases of clearcut psychoses from the use of phenobarbital as a routine. Also, in our earlier study we mentioned that phenobarbital is not a significant factor, as our patients who had received steady doses of this drug for years did not show significant losses. Paskind's group of nondeteriorated patients had been taking bromides during a period of years. It may therefore be inferred that for the majority of patients sedative medication is not the cause of deterioration. It has been the opinion of most authors that the feeling of security and the apparent reduction in attacks more than offset the possible harm from the use of such sedatives.

Restrictions in Learning.—Many a mother will protect an epileptic child from participating in activities permitted the normal child. Likewise, such children are often refused admission to schools once they have had a convulsion in the classroom. Such restrictions obviously lessen the opportunities for learning and reduce the contacts and experiences, but do not lead to deterioration.

Social and Psychologic Reactions to Epilepsy.—Throughout the ages, the term epilepsy has conveyed a stigma of degradation, abnormality and incurability. The youngster who has been refused admission to school because of having fits is publicly humiliated. As a young adult he is discharged from his job. There are idleness, unemployment and shame. The epileptic patient obviously sinks into introspection, worry, brooding and resentment. It is this psychic reaction which frequently explains the peculiar mental states of certain epileptic patients.

L. B., though suffering from epilepsy for years, has maintained a high intelligence quotient on repeated tests. On certain occasions he appears moody and disheartened. He is resentful toward society and angry with himself and the world. Such periods of ill-humor always come from the idleness, poverty and humiliation which result if he is discharged from his job because of an attack.

Our experience is in accord with the view expressed by Bridge [12] that the so-called epileptic personality represents in a large part the response of the patient to the problems and situations which the nature of the disease creates.

Diverging from the main theme of the mentality of the epileptic patient, one may mention society's indifference and neglect of the educational and occupational problems of the epileptic person. Nondeteriorated epileptic persons need more opportunities for training and for work. Every large community should provide either special schools or sheltered workshops for such persons. These more or less mentally normal patients, who need not go to colonies, require such activities—activities which may prevent the development of personality problems.

The Inherent Cerebral Disorder.—What, then, is responsible for the deterioration which certain patients manifest? It is obvious that this must be due to the basic cerebral disorder. The child suffering from Schilder's disease, the patient with dementia paralytica or a tumor of the brain and the infant with birth trauma may show progressive mental changes, corresponding to the advance of the disease processes. Of patients without obvious organic changes, Jelliffe and White [13] said:

Epilepsy may seem in many cases to produce a general mental deterioration (epileptic dementia), which may become very profound. These cases, at least many of them, on prolonged observation prove to be cases of dementia praecox with convulsive manifestations.

Most writers (see Cobb's valuable contributions [14]) have regarded epilepsy as an indicator of physiopathologic changes in the brain. The nature of this pathologic change, rather than the more conspicuous manifestation, the convulsion, is the decisive factor in deterioration.

CONCLUSIONS

Repeated tests on 35 epileptic patients made from three to eight times during a period of years showed temporary fluctuations, but on the average no steady deterioration. One patient alone presented regular losses. Some patients receiving treatment showed gains.

---

12. Bridge, E. M.: Mental State of the Epileptic Patient, Arch. Neurol. & Psychiat. **32**:723 (Oct.) 1934.

13. Jelliffe, S. E., and White, W.: Diseases of the Nervous System, Philadelphia, Lea & Febiger, 1935.

14. Cobb, S.: Causes of Epilepsy, Arch. Neurol. & Psychiat. **27**:1245 (May) 1932.

The more critical Babcock test revealed a loss of efficiency amounting to one year. This amount does not represent pathologic deterioration, but it is a loss of mental efficiency of statistical significance.

For patients who show deterioration, the basic disease responsible for the epilepsy rather than the conspicuous convulsion is the determining factor.

It is our opinion that the personality problems of an epileptic person are often due to the social and psychologic reactions to his disease rather than to any change in intelligence. It is suggested that this may be lessened by provision for training and sheltered workshops.

STUDIES IN DISEASES OF MUSCLE

VI. PROGRESSIVE PERONEAL MUSCULAR ATROPHY; REPORT ON A FAMILY, WITH STUDY OF HEREDITY AND OF METABOLISM OF CREATINE AND CREATININE

S. M. SMALL, M.D.

AND

A. T. MILHORAT, M.D.

NEW YORK

The clinical syndrome commonly referred to as peroneal muscular atrophy has been known since 1856, when Eulenburg [1] described the condition in 2 brothers. Much later, in 1873, Eichhorst [2] reported on a family in which muscular atrophy of this type had occurred in six generations. Reports of other cases were published by several authors, e. g., Schultze,[3] but it remained for Charcot and Marie,[4] Tooth [5] and Hoffmann [6] to describe the condition as a definite clinical entity. Charcot and Marie described the characteristics of the disease as slowly progressive wasting of the muscles of the feet and calves, fibrillary movements in the muscles involved, occasional defects in the perception of sensation, vasomotor disturbances and a definite hereditary predisposition to the disease. In his classic contribution, Hoffmann [6] differentiated the disease from various other types of progressive muscular wasting and stated that the condition represents a clinical entity more definite in its characteristics than are most diseases. However, as even Hoffmann showed, the findings in different patients with peroneal muscular atrophy

---

From the New York Hospital and the Department of Medicine, the Cornell University Medical College, and the Russell Sage Institute of Pathology.

1. Eulenburg, A.: Ueber progressive Muskelatrophie, Deutsche Klin. **8**: 129, 1856.

2. Eichhorst, H.: Ueber Heredität der progressiven Muskelatrophie, Berl. klin. Wchnschr. **10**:497 (Oct.) 1873.

3. Schultze, F.: Ueber eine eigenthümliche progressive atrophische Paralyse bei mehreren Kindern derselben Familie, Berl. klin. Wchnschr. **21**:649 (Oct.) 1884.

4. Charcot, J., and Marie, P.: Sur une forme particulière d'atrophie musculaire progressive, souvent familiale débutant par les pieds et les jambes, et atteignant plus tard les mains, Rev. de méd., Paris **6**:97, 1886.

5. Tooth, H.: Peroneal Type of Progressive Muscular Atrophy, London, H. K. Lewis, 1886.

6. Hoffmann, J.: Ueber progressive neurotische Muskelatrophie, Arch. f. Psychiat. **20**:660, 1889.

may vary widely in prominence. Indeed, the diagnosis will sometimes be obscure until more symptoms have developed or a study of other affected members of the family has been made.

The findings in the family described in this report are of interest because of the various ways in which the disease manifested itself in the different members. One patient presented a clinical picture simulating that of chronic anterior poliomyelitis; another showed more evidence of disturbance in sensory function than of involvement of the muscles. In most other patients in this family the wasting and weakness of the muscles were the conspicuous findings, whereas the defects in sensory function were slight. In all patients but 1 the muscles of the hands were involved early in the course of the disease. As these findings are of interest for an understanding of this condition as a definite clinical syndrome, the following report on 7 patients in one family appears desirable. A family tree showing the heredity of the disease in three generations is presented. In addition, studies on the metabolism of creatine and creatinine were made in 4 patients.

REPORT OF CASES

CASE 1.—L. G., a youth of Italian descent, aged 16, gave the following history. Four years previously, at the age of 12, he had noted that he had a tendency to invert the left foot and that he walked on the outside of the sole. This condition progressed, and soon after there developed shuffling gait, bilateral foot drop and wasting of the muscles of the calves. The feet became weak and deformed, and the muscles of both calves were observed to be smaller. The weakness of the muscles and the difficulty in walking progressed rapidly, but for the year prior to his admission to the hospital they appeared to be stationary. However, during this period both hands had become thin and weak. The grip was less powerful, and finer movements could not be made. The past personal history was noncontributory.

Examination revealed the difficulty in walking of which the patient complained. The gait was uncertain. The feet appeared to hang loosely on the legs when the patient walked and were brought to the floor with a slap. The left foot was held inverted, and the heel did not touch the floor. The muscles of the feet were weak and wasted, and all movements were restricted. There was definite foot drop with some inversion of both feet, which was more definite on the left side. The peroneal muscles were wasted and weak. The muscles of the thighs were not involved as extensively as were those of the calves, but there were considerable weakness and wasting (fig. 1). Numerous pronounced fibrillations were seen over both thighs and calves and were increased when the muscles were struck. There were moderate wasting and loss of power of the muscles of both hands. The thenar eminences were wasted, and the interosseal muscles of both hands were weak and small (fig. 2). In contrast, the muscles elsewhere were exceedingly well developed. The muscles of the shoulder girdle and upper portion of the arm were large and powerful; the platysma muscles were well developed. Over both upper extremities there were occasional fibrillations. The biceps and triceps tendon reflexes were reduced on both sides. The knee and ankle jerks were absent, and

the plantar reflexes were flexor in type. The abdominal and cremasteric reflexes were normal. No sensory defect could be detected. No tenderness was elicited when the peripheral nerves or muscles were palpated. The axillas were dripping with perspiration. The feet were slightly cyanotic and felt cold to both the patient and the examiner. A roentgenogram of the spine showed a congenital projection of the fifth dorsal segment and a false articulation with the lower rib. The Kline and Wassermann reactions of the blood were negative.

CASE 2.—G. R. (a cousin of L. G.), a girl aged 9, had complained of progressive weakness of the feet for two years. When she walked the right foot slapped

Fig. 1 (L. G.).—Wasting of the muscles of the feet, calves and thighs. The arches of the feet are high, and the heels do not touch the floor. Note the excellent development of the muscles of the chest and upper portions of the arms.

slightly on the floor. The left foot showed a moderately high arch, and both feet were held in moderate "foot drop" position. There were slight wasting of the muscles of both feet and questionable wasting of the peroneal muscles. The muscles of the trunk, upper extremities and thighs were well developed and strong. The muscles of the hands showed no wasting. The tendon reflexes of the upper extremities and the abdominal reflexes were normal. The knee jerks were much diminished, and the ankle jerks were absent. The plantar reflexes were flexor in type. No fibrillations were noted, even after repeated mechanical stimulation

of the muscles. Perception of light touch, vibration and pain were normal everywhere except over the face, where there was some diminution in the perception of pinprick.

Case 3.—F. P. (a cousin of L. G. and G. R.), a schoolboy aged 9, complained of "turning in" of the feet and inability to grasp objects strongly with the hands. At the age of 3 years he had had acute poliomyelitis, with paralysis of the muscles of the left side of the face and of both legs. The disability in the legs disappeared entirely, and the patient, after one year, was able to walk and run as well as his playmates, but moderate weakness of the muscles of the face persisted. Two years before his admission to the hospital, at the age of 7, the feet began to "turn in" and became weak. This progressed gradually. One year later he noted difficulty in grasping objects with the hands, but there seemed to be either very slow progress or none at all.

Examination revealed slight flattening of the left side of the face, with inability to close the left eye as tightly as the right. The forehead could be well wrinkled.

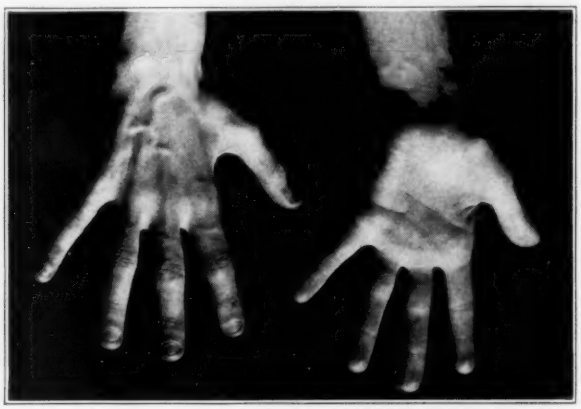


Fig. 2 (L. G.).—Wasting of the thenar and hypothenar eminences and of the interosseal muscles.

On opening the mouth the jaw deviated to the left. The tongue deviated to the left on protrusion. There was slight slurring of speech. The palatal reflex was active. The arms were symmetric, and there was no muscular wasting or adventitious movements. There was slight wasting of the interosseal muscles and of the thenar eminences, with corresponding loss of power and difficulty in holding objects. There was toe drop bilaterally, with slight inversion of the feet on walking. No fibrillations were noted. The tendon reflexes were normal; the abdominal reflexes were active and equal. No disturbance in sensory function was detected.

Case 4.—R. G. (the mother of L. G.), a housewife aged 41, complained of weakness of the hands and feet. Development of the disability had been so insidious that it was difficult to give a definite date of onset. For about ten years she had had slowly progressive difficulty in walking, and for about eight years the grasp of the hands had slowly become weaker. For from three to four years sensations of "pins and needles" had been felt in the fingers of both hands. The patient complained of the feet feeling cold, except during the warm summer months.

Examination showed a somewhat uncertain gait. The feet were brought to the floor with a slap when the patient walked. Both hands were weak, and the

grasp lacked much power. The thenar eminences were flattened, and the intrinsic muscles of both hands were weak and wasted. The peroneal muscles and the muscles of the feet showed moderate weakness and wasting. The biceps tendon reflexes were absent. The triceps reflexes were equal on the two sides, but somewhat diminished. The knee and ankle jerks were absent. Occasional fibrillary twitchings of the muscles of the calves were seen when the muscles were struck with the percussion hammer. Perception of pinprick was definitely diminished over the tips of all the fingers and moderately diminished over the rest of the hands. There were no other sensory defects.

Case 5.—M. R. (the mother of G. R.), a housewife aged 34, complained of weakness of the hands and feet. About thirteen years before her admission to the hospital she had noted slight weakness of the hands and feet, which progressed very slowly. At the time of admission she had moderate difficulty in grasping objects and holding them in the hands. There was only moderate disability in walking, but she was unable to walk fast and stated that the feet felt as if they "hung loosely" on the legs.

Examination showed the weakness of the hands and feet of which the patient complained. There was considerable wasting of the thenar eminences and the intrinsic muscles of both hands, which gave the hands a flattened, "apelike" appearance. The muscles of the feet and of both calves were moderately wasted. The feet could be moved passively in all normal directions, but the patient was unable to lift the feet actively from a toe drop position. The arches of both feet were high. All the tendon reflexes were normal except the ankle jerks, which were absent, and the knee jerks, which were moderately diminished. No adventitious movements could be seen. The perception of vibration was definitely diminished over both lower extremities below the knees and almost absent over both feet. There were no other sensory defects.

Case 6.—E. P. (the mother of F. P.), a housewife aged 33, complained of slowly increasing weakness of the hands and feet for about five years before her admission to the hospital. The disability progressed gradually, until the feet appeared to "hang loosely" on the legs and she could not control them normally in walking. For three years prior to her admission the hands had felt numb at night, with sensations of "pins and needles." There had been no paresthesia over the feet. The sensory disturbances had slowly and progressively become worse.

Examination showed that the patient walked in a guarded fashion. The feet slapped on the floor in walking, and they were often inverted. The muscles of the hands were wasted. The thenar eminences were replaced by depressions, and the hands were "apelike" in appearance. The grip was weak. The feet showed a high arch, moderate foot drop and a moderate amount of inversion. All movements of the feet were weak and were performed poorly against resistance. The peroneal muscles showed moderate wasting. The legs had a definite tapering appearance. No adventitious movements could be seen or elicited. The tendon reflexes were moderately diminished but equal on the two sides, except the ankle jerk, which was absent. Over the distal phalanges of all the fingers perception for pinprick, cotton wool, vibration and temperature was absent. Over the middle phalanges there was moderate loss of perception for these modalities. Over the hands and forearms the sensory defect decreased as the elbows were approached, and above the elbows sensation was normal. Over the toes of both feet perception for pinprick, cotton wool, vibration and temperature was almost lost; over the rest of the feet the sensory defect was slight.

CASE 7.—F. D. (a cousin of R. G. and an uncle of L. G.),[7] an unmarried man aged 37, had weakness and wasting of the muscles of the hands and feet, which had first been noted in 1934 (at the age of 34). Onset of the disability had been insidious. The course had been slowly progressive during the first year or so, but had since appeared to be stationary.

Examination revealed that the pupils were equal and reacted promptly to light and in attempts at near vision. There was right internal strabismus. There were wasting and weakness of the intrinsic muscles of both hands, especially of the interosseal muscles, and those of the thenar and hypothenar eminences. There was a suggestion of wasting of the muscles of the forearms. The patient walked on a broad base and lifted the feet high because of toe drop. Both feet showed pes cavus with toe drop. There was wasting of the intrinsic muscles of both feet, which were thin, and of the muscles of the calves as far up as the knees. The circumference of each calf was 11½ inches (29.2 cm.). The muscles of the thighs appeared not to be involved. The knee jerks were almost absent. No plantar response could be elicited. There were no fibrillary movements. The patient was too uncooperative for a detailed examination of sensation.

COMMENT

The present family is of interest because of the different ways in which the disease manifested itself in the several patients. Most of them presented a classic picture of peroneal muscular atrophy. In these patients the wasting and weakness of the muscles of the calves and feet were apparent. Deformities of the feet were conspicuous, and fibrillary twitchings in the affected muscles could be demonstrated. Slight or moderate defects in sensory perception were found in most of these patients. Involvement of the hands occurred perhaps earlier in the course of the disease than is usual.

One patient, L. G., however, presented a clinical picture closely resembling that of progressive muscular atrophy of spinal origin. The muscles of the thighs were small and weak, and although they were not involved as much as those of the calves and feet, they showed considerable muscular wasting. There was no disturbance in sensory function. Fibrillary twitchings were pronounced and numerous. It was inferred that the patient had muscular wasting subsequent to chronic anterior poliomyelitis. In contrast, another patient, M. R., had considerable disturbance in sensory function and only moderate muscular wasting. The clinical findings in this instance resembled those commonly seen in patients with peripheral neuritis. The other patients in this family showed the clinical pictures most commonly seen in peroneal muscular atrophy.

---

7. We did not examine this patient. Dr. John H. Travis, superintendent of the Creedmoor State Hospital, Queens Village, N. Y., furnished a record of his findings and gave us permission to publish the notes in this case.

Although the findings in these patients appear to differ widely, similar differences in the pathologic lesions within the nervous system have been observed by many workers. Hoffmann [6] expressed the opinion that the changes in the peripheral nerves were the primary lesion, but practically all subsequent observers described extensive changes in the spinal cord as well as in the peripheral nerves. Involvement of the cells of the anterior horns of the spinal cord was observed by Dejerine and Armand-Delille,[8] Marinesco,[9] Siemerling,[10] Sainton [11] and others. Gombault and Mallet,[12] Marinesco [9] and Sainton [11] observed atrophy of the cells of the posterior horns, but the last two workers did not note involvement of the pyramidal tracts. In the cases of Sainton and Siemerling the spinal ganglia showed definite changes, and in those of Dejerine and Armand-Delille and Marinesco the posterior roots were affected. However, the most common lesion within the nervous system was in the peripheral nerves, in the peripheral portions of which the process usually was more advanced. It is difficult to evaluate the various pathologic changes, since most of the material was obtained from patients who had had the disease for many years and many changes within the nervous system might have developed subsequent to the initial lesion. However, the frequency with which definite changes have been observed in the spinal cord as well as in the peripheral nerves leaves little doubt that in peroneal muscular atrophy the process involves both the peripheral nerves and different parts of the spinal cord, but in varying degrees.

The clinical findings in peroneal muscular atrophy may occasionally be confused with those of peripheral neuritis (e. g., in M. R.). This similarity in the clinical picture has its counterpart in the pathologic changes in the nervous system. Marinesco [13] concluded that these changes are of the same kind in the two conditions. In cases of peripheral neuritis secondary to a variety of factors, changes within the spinal cord have been described. Heilbronner [14] showed that in alcoholic poly-

8. Dejerine, J., and Armand-Delille, P.: Un cas d'atrophie musculaire, type Charcot-Marie, suivi d'autopsie, Rev. neurol. **11**:1198, 1903.

9. Marinesco, G.: De l'amyotrophie Charcot-Marie, Arch. de méd. expér. et d'anat. path. **6**:921, 1894.

10. Siemerling, E.: Zur Lehre der spinalen neuritischen Muskelatrophie (Atrophia muscularis progressiva spinalis neuritica Bernhardt) (progressiven neurotischen oder neuralen Muskelatrophie Hoffmann), Arch. f. Psychiat. **31**:105, 1898.

11. Sainton, P.: Contribution à l'étude anatomo-pathologique et clinique de l'amotrophie Charcot-Marie, Nouv. iconog. de la Salpêtrière **12**:206, 1899.

12. Gombault, A., and Mallet, H.: Un cas de tabès ayant débuté dans l'enfance: autopsie, Arch. de méd. expér. et d'anat. path. **1**:385, 1889.

13. Marinesco, G.: Contribution à l'étude anatomo-clinique de l'amyotrophie Charcot-Marie, Rev. neurol. **2**:543 (Oct.) 1928.

14. Heilbronner, K.: Rückenmarksveränderung bei der multiplen Neuritis der Trinker, Monatschr. f. Psychiat. u. Neurol. **3**:469, 1898.

neuritis the cells of the anterior and posterior horns of the spinal cord are affected, and Haupt and Dobberstein [15] observed similar involvement of the posterior and anterior horns in experimental polyneuritis in fowls. In their studies on the production of polyneuritis following the use of phenol esters, Lillie and Smith [16] observed degenerative changes in the spinocerebellar, rubrospinal, vestibulospinal and tectospinal tracts of the spinal cord, in addition to partial degeneration of the peripheral nerves. In a more recent investigation of the changes in the spinal cord occurring in polyneuritis, Accornero [17] concluded that these changes are in part secondary and in part primary. He expressed the belief that the factor causing the disease affects the peripheral nerves and also parts of the spinal cord. This opinion appears to be justified on the basis of his own observations and those of Haupt and Dobberstein and Lillie and Smith. The postulation of a process affecting both the spinal cord and the peripheral nerves in peroneal muscular atrophy would explain the differences in the findings sometimes observed in this condition. No histologic evidence can be offered in the cases reported here, but it is likely on the basis of the clinical data that such a postulation could account for the different symptoms and findings shown by the 7 patients in this family. This does not imply that the mechanism of the disease process is the same in peroneal muscular atrophy as that in peripheral neuritis. In the former condition the role of heredity is of obvious importance. Whether peroneal muscular atrophy is due to an abiotrophy of certain tissues in the nervous system or whether persons inheriting the factor have a nervous system especially susceptible to the influence of certain agents or metabolic processes is not known. Nor is it known that the changes in the nervous system are not secondary to some inherited metabolic defect. In the present state of knowledge, the admission of ignorance is the safest course.

Aring and Cobb,[18] in a classification of the diseases of muscle, called peroneal muscular atrophy a subvariety of the myelopathic familial myopathy group. They included in this group infantile muscular atrophy of the Werdnig-Hoffmann type, hypertrophic neuritis and Friedreich's ataxia. In all these familial diseases involvement of the neuraxis is observed.

---

15. Haupt, H., and Dobberstein, J.: Ein Beitrag zur Polyneuritis des Geflügels, Ztschr. f. Infectionskr., par Krankh. u. Hyg. d. Haustiere **31**:58 (March 31) 1927.

16. Lillie, R. D., and Smith, M. I.: Histopathology of Some Neurotoxic Phenol Esters, National Institute of Health Bulletin 160, United States Treasury Department, Public Health Service, 1932.

17. Accornero, F.: Zur Frage der Rückenmarksveränderungen bei Polyneuritis, Deutsche Ztschr. f. Nervenh. **143**:137, 1937.

18. Aring, C. D., and Cobb, S.: The Muscular Atrophies and Allied Disorders, Medicine **14**:77 (Feb.) 1935.

The data in this report are not sufficient to permit a discussion of any of the biologic relations among these various clinical syndromes. However, the observations are in agreement with the formulation of Aring and Cobb [18] that the disease process in peroneal muscular atrophy may involve different parts of the spinal cord and peripheral nerves in varying degrees and thus produce manifold clinical and pathologic changes.

HEREDITARY TRANSMISSION

Figure 3 shows the inheritance of the disease through three consecutive generations. One or more descendants of all the affected parents showed definite evidence of the disease. On the other hand, in all instances in which both parents were free from the disease all the

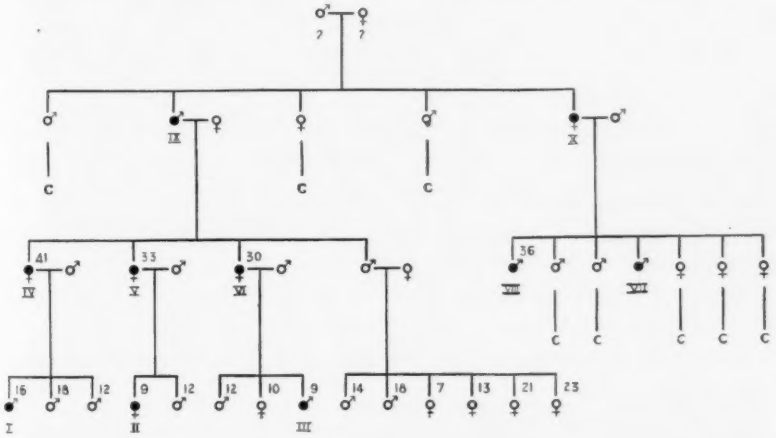


Fig. 3.—Family tree showing hereditary transmission of peroneal muscular atrophy through three generations of one family.

The solid black circles indicate the persons who showed evidence of the disease. The ages of the persons are shown by the arabic numerals. The roman numerals indicate the case numbers of the patients. *C* represents children without the disease.

progeny likewise were free from any evidence of the condition. It appears from this that the hereditary factor for peroneal muscular atrophy is dominant, for, in this family at least, the disease does not manifest itself in any offspring without having been discernible in one of the parents. Whether or not the hereditary factor is also sex linked cannot be determined by the data available. The cases are too few to rule out this possibility. Macklin and Bowman [19] found that approximately half the offspring of affected parents showed symptoms of the

19. Macklin, M. T., and Bowman, J. T.: Inheritance of Peroneal Atrophy. J. A. M. A. **86**:613 (Feb. 27) 1926.

disease. They concluded that the condition is transmitted probably by a unit hereditary character, in other words, that the gene or genes determining the inheritance of the disease are carried in one chromosome.

On the other hand, Herringham [20] observed in his series that only males were affected and that the disease was transmitted by females who showed no symptoms of the condition. Therefore, in his patients the hereditary factor was both recessive and sex linked. Although Macklin and Bowman [19] stated that there is doubt regarding the classification of the cases reported by Herringham, it is likely that the hereditary factor for progressive peroneal muscular atrophy can be transmitted in more than one way. The situation may be similar to that observed by Wolff and one of us (A. T. M.)[21] in cases of progressive muscular dystrophy. In some instances of the latter condition the hereditary factor was found to be recessive; in others it was both recessive and sex linked, and in one family the factor was dominant.

METABOLISM OF CREATINE AND CREATININE

The metabolism of creatine and creatinine was studied in 4 patients according to the methods described in the earlier reports of Wolff and one of us (A. T. M.).[22] During a period in which the patients were maintained on a diet free from creatine and creatinine the daily urinary output of creatine and creatinine was determined. After an adequate period which served as a control a test dose of creatine (1.32 Gm.) was given, and the ability of the patient to retain the ingested creatine was estimated. The percentage amount of creatine retained is referred to as the creatine tolerance.

Only 2 of the 4 patients (table) excreted creatine spontaneously. One patient, L. G., with considerable muscular disability, eliminated only 0.025 Gm. of creatine daily, an amount commonly considered to be normal. G. R., a girl aged 9, excreted only minimal amounts (0.011 Gm.) of creatine daily. Since normal children of the same age often excrete fairly large amounts of creatine, the small amounts eliminated by this patient cannot be related to the moderate amount of muscular disability which she had. In an earlier report (Milhorat and Wolff [22]), it has been shown that in patients with muscular wasting subsequent to disease of the nervous system considerable muscular disability can

20. Herringham, W. P.: Muscular Atrophy of the Peroneal Type Affecting Many Members of the Same Family, Brain **11**:230, 1889.

21. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscles: Mechanism of Heredity in Progressive Muscular Dystrophy; Relation Between Age of Onset and the Clinical Course, to be published.

22. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscles: IV. Metabolism of Creatine and Creatinine in Muscular Wasting Subsequent to Disease of the Nervous System, Arch. Neurol. & Psychiat. **40**:663, 1938.

occur with little effect on the output of creatine or the creatine tolerance so long as the muscles affected represent only a portion of the muscle mass of the body. However, when most of the voluntary muscles of the body are involved serious defects in the metabolism of creatine occur.

In the cases reported here, the muscles affected were of considerable clinical importance, but they represented only a small fraction of the striated musculature of the body. Neither the output of creatine nor the creatine tolerance was of a value that could be considered abnormal for persons of the same age and sex.

Likewise, the output of creatinine showed no significant variation from the normal. The creatinine index [23] for some patients appeared to be high (e. g., 31.2 for L. G.). However, these high values are explained by the excellent development of the muscles which were not involved. The large amounts of creatinine which well developed per-

Spontaneous Output of Creatinine and Creatine and the Creatine Tolerance in 4 Patients with Peroneal Muscular Atrophy

Case No.	Patient	Sex	Age, Yr.	Weight, Kg.	Height, Cm.	Daily Urinary Creatinine,* Gm.	Daily Urinary Creatine, Gm.	Creatinine Coefficient†	Creatine Tolerance,‡%
1	L. G.	M	16	53	165	1.650	0.025	31.2	92
4	M. R.	F	34	72	160	1.400	0	19.5	86
5	F. P.	M	9	37	144	0.950	0	27.7	70
6	G. R.	F	9	31	...	0.783	0.011	25.2	63

* Preformed creatinine.
† The creatinine coefficient is expressed as the number of milligrams of preformed creatinine per kilogram of body weight.
‡ The creatine tolerance is the percentage retention of ingested creatine (1.32 Gm.).

sons excrete normally would mask whatever slight reduction might result from the loss in muscle mass. It has been shown that in muscular wasting subsequent to involvement of the nervous system the diminution in the output of creatinine is related to the reduction in the amount and efficiency of the total muscle mass (Milhorat and Wolff [22]).

SUMMARY

Seven cases of peroneal muscular atrophy in three generations of a family are reported.

Five of the patients presented the clinical picture commonly seen in this condition. However, in 1 patient the findings resembled those of chronic progressive poliomyelitis, and in another patient the defects in sensory perception were the outstanding changes.

The hereditary factor in this family appeared to be dominant.

In spite of considerable wasting of important muscle groups, the metabolism of creatine showed little involvement.

23. The creatinine index is the number of milligrams of daily urinary creatinine per kilogram of body weight.

THE ELECTROENCEPHALOGRAM IN BROMIDE INTOXICATION

MORTON A. RUBIN, PH.D.
AND
LOUIS H. COHEN, M.D.
WORCESTER, MASS.

Estimation of the quantity of toxic substance sufficient to induce clinical symptoms of involvement of the nervous system is difficult. This is the case in bromide intoxication, in which the threshold of toxicity is extremely variable in different persons. Individual differences may account in one person for absence of symptoms at a level of bromide in the blood which would be associated in another person with marked toxic symptoms. In the present study the electroencephalogram of a patient with bromidism was studied as a neurophysiologic index of the degree of bromide intoxication. Changes in the electrical activity of the brain, as measured by this means, form a delicate index of disturbances in the normal "resting" activity of spontaneously beating neurons.

Many factors, such as lesions of the brain (Lemere [1]), drugs (Gibbs, Gibbs and Lennox [2]), tumors (Walter [3]), insulin shock (Hoagland, Rubin and Cameron [4]) and epilepsy and conditions of impaired consciousness (Gibbs, Davis and Lennox [5]), influence the spontaneous electrical activity of the brain. One of the characteristic features of the human electroencephalogram is the alpha rhythm, of 10 cycles per second, recorded from the occipital lobes when the subject's eyes are

---

From the Biological Laboratories, Clark University, and the Research Service, the Worcester State Hospital.

This investigation was aided by a grant from the Child Neurology Research (Friedsam Foundation).

1. Lemere, F.: Berger's Rhythm in Organic Lesions of the Brain, Brain **60**:118-125, 1937.

2. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Effects on the Electro-Encephalogram of Certain Drugs Which Influence Nervous Activity, Arch. Int. Med. **60**:154-166 (July) 1937.

3. Walter, W. G.: The Electro-Encephalogram in Cases of Cerebral Tumor, Proc. Roy. Soc. Med. **30**:579-598, 1937.

4. Hoagland, H.; Rubin, M. A., and Cameron, D. E.: Electrical Brain Waves in Schizophrenics During Insulin Treatments, J. Psychol. **3**:513-519, 1936.

5. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electro-Encephalogram in Epilepsy and Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133-1148 (Dec.) 1935.

closed. It is reasonable to suppose that the alpha rhythm, and probably other features of the electroencephalogram, would be altered in the presence of bromidism.

The present study concerns a woman aged 43 who had been given large doses of bromide by a physician for increasing "nervousness" prior to admission to the Worcester State Hospital. After treatment with sodium chloride and overhydration was begun, the bromide level of the blood dropped rapidly from its initial value of 150 mg. to 24.6 mg. per hundred cubic centimeters.[6] Electroencephalograms were obtained every other day for two weeks.

ELECTROENCEPHALOGRAPHIC METHOD

A capacity-coupled amplifier, with a time constant of 0.2 second, in conjunction with a cathode ray oscillograph and an ink-writing undulator, was used to record the brain potentials. A constant amplification of 50 microvolts per 7.5 mm. of deflection was maintained throughout. The recording electrodes consisted of flattened pellets of lead solder, from 2 to 3 mm. in diameter, attached to fine, enamel-insulated copper wire. The lead electrode was placed about 2 cm. above the inion, covered with Sanborn electrode paste and fixed to the scalp with collodion. Electrodes placed behind both ears and fastened in place by strips of surgical tape were joined to form a common "indifferent" lead.

The patient reclined on a bed, with the eyes closed and covered with a towel in order to keep out all light while the records were taken.

RESULTS

When the first record was taken the bromide level of the blood was 59.6 mg. per hundred cubic centimeters. At this time the alpha frequency was 8.3 per second. Over the two week period the bromide level fell from 59.6 to 36.4 mg. per hundred cubic centimeters. Accompanying this fall in the bromide level during the first eight or nine days was a progressive increase in the frequency of the alpha rhythm to 10.9 per second. The variability on a given day was very small (approximately 1 cycle). Figure 1 presents representative tracings taken during this period. The alpha frequency thenceforth remained above 10 per second for approximately another week, after which the patient became so uncooperative that it was impossible to obtain further satisfactory records. The bromide level of the blood continued to fall and reached a level of 24.6 mg. per hundred cubic centimeters at the end of the third week.

The percentage of the record which was occupied by the alpha rhythm (per cent time alpha) was found to increase from an initial level of 50 to that of 85 per cent during the first week, decreasing and remaining at from 70 to 75 per cent for the next week.[7] It was also found that the amplitude of the alpha

6. The bromide level of the blood was determined by a modification of the method of O. Wuth (Rational Bromide Treatment: New Methods for Its Control, J. A. M. A. **88**:2013-2017 [June 25] 1927).

7. A range of from 70 to 85 per cent is well within the normal limits of variability (Rubin, M. A.: A Variability Study of the Normal and Schizophrenic Occipital Alpha Rhythm, J. Psychol. **6**:325-334, 1938).

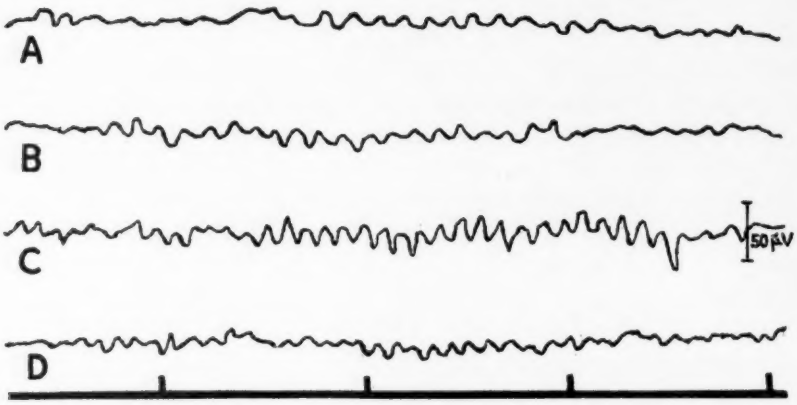


Fig. 1.—Changes in alpha frequency accompanying a progressive decrease in the bromide level of the blood. In *A* (August 5) the bromide level of the blood was 59.6 mg. per hundred cubic centimeters; in *B*, (August 6) it was not determined; in *C* (August 9) the bromide level was 47.6 mg., and in *D* (August 13), 36.4 mg. Vertical lines at the bottom give the time in seconds. The vertical line at the end of strip *C* indicates the deflection of the ink-writing undulator produced by a 50 microvolt signal.

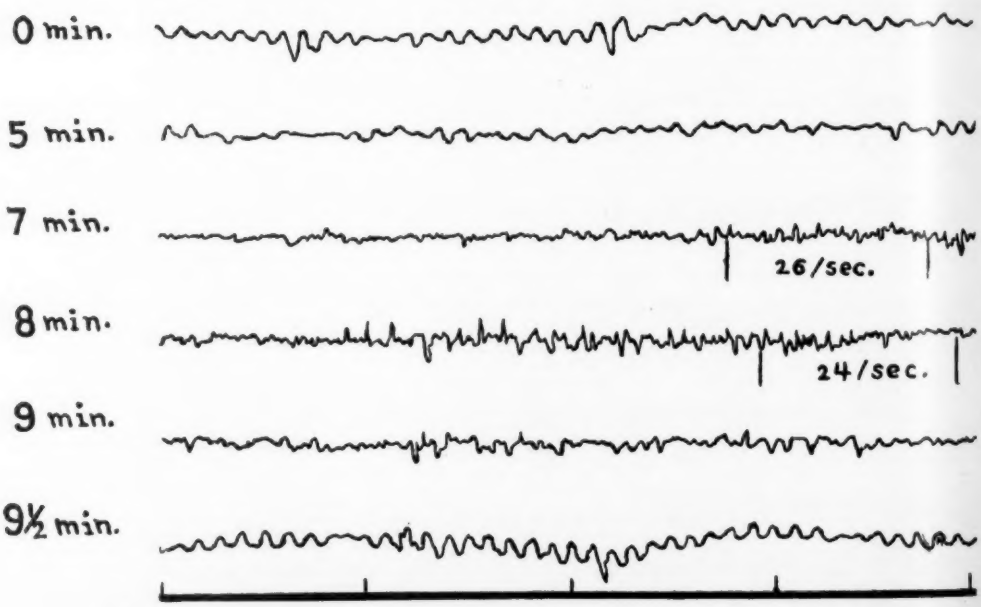


Fig. 2.—Appearance and disappearance of the beta rhythm. The tracing at the top illustrates the pattern at the beginning of the record. At *5 min.* the alpha rhythm was reduced in amplitude, and at *7 min.* practically no alpha waves were present. At *8 min.* only the 25 per second beta rhythm was seen. At *9 min.* the beta rhythm began to break up, and an alpha rhythm reappeared. From *9½ min.* to the end of the record (twenty minutes) only the alpha rhythm was present. The bromide level of the blood was about 35 mg. per hundred cubic centimeters. Time is expressed in seconds. The calibration is the same as that in figure 1.

cycles increased as the per cent time alpha increased. The greatest per cent time alpha (85) can be seen in record *C* of figure 1; it may be noted that the average amplitude of the alpha waves is greater than that in any of the other three strips. The relation between amplitude and per cent time alpha has been noted in many other instances;[8] a theoretical explanation of this relation will be offered in a later paper.

During the course of this study, another phenomenon was observed. On one experimental day, when the bromide level of the blood was 34.6 mg. per hundred cubic centimeters, the electroencephalogram showed a predominating twenty-five per second (beta) rhythm, which lasted for several minutes and then disappeared completely. In the legend for figure 2 the appearance and disappearance of the beta rhythm are described. The beta rhythm ordinarily is not conspicuous in the occipital lobes, especially with the placement of electrodes which we used, and we could not relate this peculiar record to anything in the patient's behavior.[9]

COMMENT

The usual sedative effect of bromides as indicated by the electroencephalogram was not observed in our records. Lennox, Gibbs and Gibbs[10] found that the intravenous injection of 30 grains (1.94 Gm.) of sodium bromide was effective in abolishing or modifying the electroencephalographic patterns of petit mal seizures. This dose was not sufficient to modify the electroencephalogram during normal intervals in these epileptic patients. Gibbs, Gibbs and Lennox[2] also reported that sodium bromide (30 grains; 1.94 Gm.) administered intravenously to 8 subjects brought about no change in the electroencephalogram when sleep or drowsiness was not produced. In patients with a maximum sedative effect the electroencephalogram characteristic of sleep was observed.[11] The patient described in this paper did not show any of the slower rhythms characteristic of sedation or sleep.

It is a common observation that the alpha frequency is remarkably constant for a given person even over long periods, seldom varying by more than 1 cycle. The characteristic frequency for different persons may be as low as eight per second or as high as twelve or thirteen per

8. Rubin, M. A.: The Distribution of the Alpha Rhythm over the Cerebral Cortex of Normal Man, J. Neurophysiol. **1**:313-323, 1938.

9. Blake, H., and Gerard, R. W.: Brain Potentials During Sleep, Am. J. Physiol. **119**:692-703, 1937. These authors stated that fast rhythms may be associated with muscular tone or movement. On the day that the marked beta rhythm occurred, we observed nothing superficially different in the muscular tension of the patient; if anything, she was more relaxed than usual. We do not believe that these fast waves represented a subclinical seizure, since there was nothing in the patient's history suggestive of epilepsy.

10. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: Effect on the Electro-Encephalogram of Drugs and Conditions Which Influence Seizures, Arch. Neurol. & Psychiat. **36**:1236-1250 (Dec.) 1936.

11. In sleep the alpha rhythm drops out and is replaced eventually by rhythms of from ½ to 3 per second.

second. Unlike metabolic stimulants, such as thyroxin (Rubin, Cohen and Hoagland [12]), and heat (Hoagland [13]), most drugs do not increase the alpha frequency in the normal person. On the other hand, it is easy to decrease the alpha frequency or to abolish it entirely. These facts seem to indicate that in the normal person the processes responsible for the alpha frequency [14] are taking place at, or nearly at, their optimal physiologic rate. If such is the case, it follows that an alpha frequency of eight per second in a person characteristically showing a frequency of thirteen per second indicates interference with the processes normally responsible for this activity. Further, a lowered alpha frequency is indicative of a decrease in the metabolic rate of the cortical cells (Rubin and others; [12] Hoagland,[13] and Hoagland, Rubin and Cameron [15]). From this, it seems that a major effect of bromide intoxication is interference with processes normally controlling the frequency of the alpha cycles.

We interpret the alpha frequency of from ten to eleven per second as that characteristic for our patient under normal conditions. Frequencies significantly lower than these must be regarded as abnormal and, in this instance, as an effect of bromide intoxication. It is of interest that an alpha frequency of ten and nine tenths per second was associated with a bromide level of the blood of 36.7 mg. per hundred cubic centimeters; this agrees with the observation of Gibbs and his associates [16] that 30 grains of sodium bromide given intravenously (which corresponds to a bromide level of from 35 to 40 mg. per hundred cubic centimeters of blood) had no effect on the electroencephalogram of normal persons or of epileptic subjects during normal intervals. This observation lends support to our inference that when the alpha frequency had reached a steady high level the physiologic intoxication due to the bromide had almost, if not completely, disappeared. It also supports our contention that an alpha frequency of from ten to eleven per second was normally characteristic for this person. It appears that with such an alpha frequency any involvement of the brain tissue due to bromidism

12. Rubin, M. A.; Cohen, L. H., and Hoagland, H.: The Effect of Artificially Raised Metabolic Rate on the Electroencephalogram of Schizophrenic Patients, Endocrinology **21**:536-540, 1937.

13. Hoagland, H.: Pacemakers of Human Brain Waves in Normals and in General Paretics, Am. J. Physiol. **116**:604-615, 1936.

14. Hoagland, H.: Some Pacemaker Aspects of Rhythmic Activity in the Nervous System, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., Biological Laboratory, 1936, vol. 4, pp. 267-276. The relation of physiologic rhythms to continuous chemical events is discussed.

15. Hoagland, H.; Rubin, M. A., and Cameron, D. E.: The Electroencephalogram of Schizophrenics During Insulin Hypoglycemia and Recovery, Am. J. Physiol. **120**:559-570, 1937.

16. Gibbs; Gibbs and Lennox.[2] Blake and Gerard.[9]

which may have remained was insignificant—surely, not sufficient to be considered of importance in the production of toxic symptoms.

The mechanism of the alteration in the per cent time alpha by bromides is not readily explainable at present and must wait for elucidation. It is probably of a different nature from that involved in the control of alpha frequency, since in general there seems to be no correlation between per cent time alpha and alpha frequency, according to our observations and those of others.

We have purposely refrained from mentioning any relation between the electroencephalogram and psychosis. With the method outlined here, one can ascertain merely the presence or absence of physiologic bromide intoxication. This, in itself, should be of assistance in the interpretation of the clinical symptoms associated with bromide intoxication, especially in evaluation of the degree to which the intoxication contributes to the psychosis, if present. If toxic conditions associated with other drugs similarly manifest their effects in the electroencephalogram, this approach may have an even broader application. We propose to continue our investigations along these lines.

SUMMARY

A case of bromide intoxication is described in which electroencephalograms revealed that the alpha frequency was low at a bromide level of 59.6 mg. per hundred cubic centimeters of blood, but rose appreciably and was maintained at a higher frequency when the bromide level reached 36.7 mg. The alteration in alpha frequency accompanying the decrease in the bromide level of the blood is attributed to changes in the metabolic rate of the cortical (occipital) neurons studied. The percentage of the record occupied by the alpha rhythm and the average amplitude of the alpha cycles also rose to a consistently high level as the bromide level of the blood decreased. In one instance a dominant beta rhythm was observed. It is suggested that the electroencephalogram may be of use in ascertaining the presence or absence of physiologic bromide intoxication, and possibly of toxicity due to other agents.

LATE DAMAGE FROM ROENTGEN IRRADIATION OF THE HUMAN BRAIN

W. SCHOLZ, M.D.
MUNICH, GERMANY
AND
Y. K. HSÜ, M.D.
PEIPING, CHINA

The heads of 3 deteriorated young patients with schizophrenia were irradiated for the purpose of investigating the effect of roentgen rays on the permeability of the barrier between the blood and the cerebrospinal fluid.[1] Exposure was made through six portals, with a 180 to 270 per cent erythema skin dose for each portal, calculated to give an even distribution through the brain of about 400 per cent erythema skin dose.[2] Each course was completed in three days. There was some indication in 2 cases that the permeability was increased at the end of four and one-half and six and one-half weeks, respectively, after irradiation, which seems to parallel the histologic changes in the *Frühreaction* of irradiated dogs, as described by one of us (W. S.).[3]

There remains to be determined whether the dose and timing of the roentgen exposures were safe from the standpoint of late damage to the brain. These patients were followed in the Municipal Psychopathic Hospital, Peiping. Two of them died about seventeen and one-half and nineteen months, respectively, after irradiation. During life the mental picture had remained unchanged; general health declined steadily, but the patients did not present any focal signs except for general

---

From the Deutsche Forschungsanstalt für Psychiatrie, Munich, Germany, and the Division of Neuropsychiatry of the Department of Medicine, Peiping Union Medical College, Peiping, China.

1. Hsü, Y. K.; Chang, C. P.; Hsieh, C. K., and Lyman, R. S.: Effect of Roentgen Rays on the Permeability of the Barrier Between Blood and Cerebrospinal Fluid, Chinese J. Physiol. **10**:379, 1936.

2. The roentgen factors were as follows: 180 kilovolts and 8 milliamperes; skin target distance, 50 cm.; filters, 56 mm. of oil, 6.25 mm. of copper and 2 mm. of aluminum; effective wavelength, 0.195 angstrom units; half value layer, 0.67 mm. of copper; dose, 28 roentgens per minute (800 roentgens measured in air is taken as a 100 per cent erythema skin dose), and portals, from 80 to 150 sq. cm.

3. Scholz, W.: Ueber die Empfindlichkeit des Gehirns für Röntgen- und Radiumstrahlen, Klin. Wchnschr. **14**:189, 1935; Experimentelle Untersuchungen über die Einwirkung von Röntgenstrahlen, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:765, 1934.

rigidity and becoming bedridden shortly before death. This paper reports the postmortem changes in the central nervous system of these 2 patients.

REPORT OF PATHOLOGIC CHANGES

CASE 1.—The body was that of a man aged 26. The clinical impression was catatonic schizophrenia and cicatrization of the scalp, due to roentgen radiation. Autopsy was performed four days after death. The scalp was shiny and cicatrized, with a bunch of hair left only on each temporal region and the lower occipital region. The outer surface of the skull was normal, while the inner surface showed an oval erosion, 3 by 3 by 4 mm., at the vertex, about 2 cm. to the left of the midline. The sphenoid and temporal bones in the middle fossa appeared to be porous. The dura was firmly adherent to the pia-arachnoid in the right parieto-occipital region. The brain was symmetric, weighed 1,415 Gm. and measured 18.5 cm. in the fronto-occipital length. The gyri in general were slightly flattened. Over the right parieto-occipital region was a patch of yellowish discoloration,

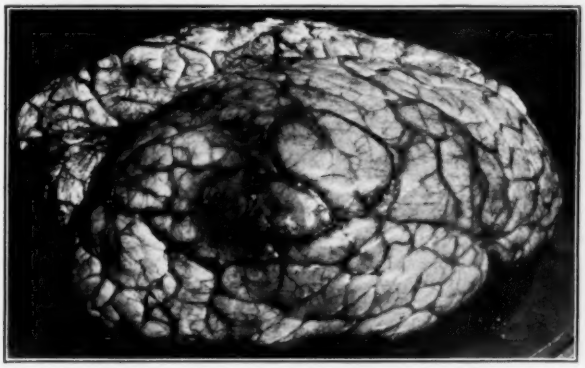


Fig. 1 (case 1).—Picture showing a dark gray patch on the right parieto-occipital cortex, which appeared yellowish red in the specimen.

5 by 5 cm., with thickening of the meninges, engorgement of the blood vessels and many hemorrhagic spots in the posteroinferior part. However, this patch presented the same consistency as other parts of the brain (fig. 1). The basal arteries were normal. Frontal sections revealed extensive necroses, varying in age, size and severity, in the cerebral white substance, the basal ganglia, the thalamus and the ependyma of all the ventricles, but none was old enough for scar formation. These changes were particularly pronounced in the occipital region and cornu ammonis of both sides, where the tissue in places had disappeared. The white substance of the right parieto-occipital region was yellowish brown, waxy, spongy and mixed with numerous hemorrhagic spots. The hemorrhages extended continuously into the cortical gray substance in several places, on the one hand, and into the basal ganglia and thalamus, except for a part of the putamen, on the other. The left basal ganglia, thalamus and adjacent white substance were similarly, but much less, involved (fig. 2). There was no dilatation of the ventricles. The cerebellum, pons, medulla and spinal cord were not remarkable.

Histologic Observations.—In most places the pia showed moderate proliferation of fibroblasts and slight infiltration with lymphocytes and phagocytes. In

addition to slight dropping out, the cerebral ganglion cells showed swelling and chromatolysis of the cytoplasm, with the nuclei either elongated, eccentric and pyknotic or not altered at all. In the white substance of the cerebrum there were small fresh necroses, with moderate or no reaction of the granular cells. A slight

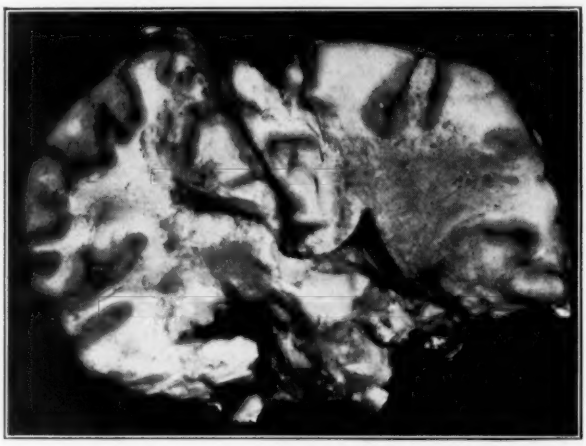


Fig. 2 (case 1).—Frontal section through the caudal part of the thalamus, showing diffuse softening and punctiform hemorrhages in the white matter and thalamus, more severe on the right side than on the left.

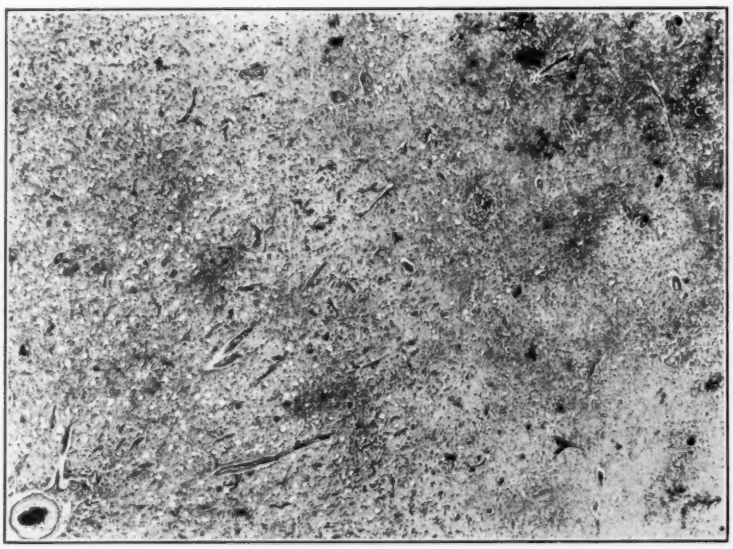


Fig. 3 (case 1).—Photomicrograph showing marked fibrosis of the pial and intracerebral blood vessels. Mallory's aniline blue stain; × 24.

progressive change of Hortega cells throughout the brain and many ameboid astrocytes in the white substance were also noted.

Focal destruction of the tissue at various stages was demonstrated in several places. The lesions in the temporal region and the medial nucleus of the thalamus

were rather fresh, while those in the parietal region, particularly the white substance, the lateral nucleus of the thalamus and the substantia nigra showed a tendency toward organization. The fresh lesions were characterized by complete destruction of the tissue, with or without tiny hemorrhages. The subacute changes showed, on the other hand, extensive demyelination in the form of swelling of the sheath and formation of myelin balls and dustlike material (Spielmeyer's stain), accumulation of fatty granular cells (scarlet red) and slight proliferation of the blood vessels.

In addition, a marked degree of fibrosis of the blood vessels was noted not only in the areas of necrosis but also in the meninges. It far exceeded the extent of necrosis of the tissue and could be beautifully demonstrated by Van Gieson's method and Mallory's aniline blue stain (fig. 3). In the area of necrosis there was also a homogeneous substance arranged in streaks or whorls in the lumens or walls of or outside the vessels. This peculiar substance stained bright reddish brown with Van Gieson's method, orange-red with congo red and dark red with Mallory's aniline blue technic. The same change was shown in the meningeal blood vessels. These vessels showed also lymphocytic infiltration and accumulation of granular cells in the adventitia and splitting and fragmentation of the elastic fibers (Weigert's method).

The choroid plexus near the cornu ammonis was sclerosed. No definite astrocytic fibers in the necrotic areas were demonstrated by Holzer's method.

The pons, medulla, cerebellum and spinal cord showed no remarkable changes.

Case 2.—The body was that of a man aged 32. The clinical impression was catatonic schizophrenia and roentgen ulcer of the scalp. Autopsy was performed four months after embalming by injection of formaldehyde into the femoral artery and cisterna magna. As shown in the illustration (fig. 4), the ulcer of the scalp was so extensive that most of the skull was exposed. There was a bunch of hair only on each temple. The edge of the ulcer was dark, rough and thick, as if burned by fire. The exposed portion of the skull showed scattered dark flecks. The inner surface of the skull at the vertex was porous, with the periosteum partly destroyed; the dura showed patches of yellowish discoloration and hemorrhages on the under surface. The brain was normal in shape, size and consistency. The pia-arachnoid appeared to be dull, but contained no exudate or hemorrhages. One large pial vein at the right sylvian fissure showed thrombosis. The arteries remained patent and presented no evidence of arteriosclerosis. Frontal sections revealed marked necroses in the occipital white substance of both sides and discrete small areas of necrosis in other parts of the cerebral white matter. The ventricles were slightly enlarged, but symmetric. The choroid plexus, basal ganglia, thalami, mesencephalon, pons, medulla, cerebellum and spinal cord showed no gross pathologic change.

Histologic Observations.—The subarachnoid meshes contained a few polymorphonuclear cells, granular cells, pigmented phagocytes and red blood cells. The cortical ganglion cells were diffusely lost, while those remaining showed either ischemic changes or swelling and chromatolysis of the cytoplasm and eccentricity of the nucleus. The cerebral white substance showed slight lymphocytic infiltration of the blood vessels and fresh tiny necroses, with little reaction of the granular cells.

There were small foci of severe, incomplete necrosis in the pallidum, putamen and adjacent external capsule on the left side. These lesions presented a satisfactory attempt at *Abbau,* as evidenced by accumulation of gemästete cells and

fat-containing granular cells. The right cornu ammonis and temporal gray substance, where the pial veins were thrombosed, showed extensive severe and ischemic cell changes, accompanied by beautiful incrustations and fresh diapedesis without glial reaction.

Fig. 4 (case 2).—Picture showing the extent and character of the roentgen ulcer on the scalp.

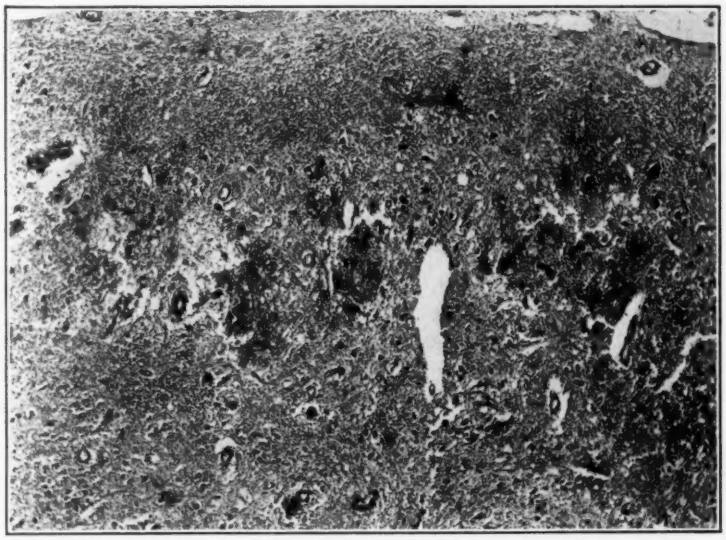


Fig. 5 (case 2).—Photomicrograph of the left geniculate body, showing irregular distribution of a homogeneous substance impregnating the walls of the vessels and the surrounding nerve tissue. Congo red stain; × 44.

In the region of the left lateral geniculate body, where the nerve tissue was preserved, the blood vessels and the tissue presented a peculiar appearance. The elastic fibers, as stained by Weigert's method, showed splitting and dispersion of homogeneous gray masses, which could be seen even around the walls of the

vessels. In Mallory's aniline blue preparations these substances in the walls of the vessels and the surrounding tissue stained uniformly red. In these places the congo red picture showed irregular distribution of homogeneous red substance impregnating the walls of the vessels and the surrounding nerve tissue (fig. 5).

Some of the blood vessels in the neighborhood of the necroses in the left lenticular nucleus and external capsule showed granular cells in the lumen or intima and lymphocytic infiltration of the media and adventitia. Scarlet red revealed bright red globules in the lumen and a uniform red reaction of the elastic layer. A blood vessel completely surrounded by a refractory homogeneous band stained uniformly reddish brown with Van Gieson's method and pink with hematoxylin and eosin.

Some of the pial blood vessels of the cerebrum showed foam cells in the place of the endothelial lining and homogeneous substance in the lumen.

Examination of a portion of the scalp taken from the edge of the ulcer revealed lymphocytic infiltration and numerous diapedeses, with little tendency to form granulation tissue. At the edge the tissue, including the blood vessels, stained uniformly orange-red with Mallory's aniline blue method and homogeneously pink with hematoxylin and eosin, resembling hyalin.

The dura showed lymphocytic infiltrations and multiple diapedesis, but was otherwise not remarkable.

The mesencephalon, pons, medulla, cerebellum, choroid plexus and spinal cord were essentially normal.

REVIEW OF LITERATURE AND COMMENT

Because of its mildness and transitory nature, the early reaction of the human brain to roentgen rays has not yet been demonstrated histologically. However, the late effect has been known since the report of a case by Fischer and Holfelder [4] and another by Markiewicz.[5] Fischer's case was one of flat epithelial carcinoma of the skin in the temporal region. The patient was treated with radiation of about 7 erythema skin doses for one year. He remained healthy until seven years later, when symptoms of focal epilepsy appeared. Biopsy of the brain tissue revealed marked destruction of the cortical architecture, great loss and alteration of the ganglion cells, edema of the interstitial tissue, thickening of the intracerebral blood vessels, structureless substances suggesting hyalin or amyloid around the vessels and numerous old hemorrhages and necroses. In Markiewicz' case, jacksonian epilepsy developed five years after the first irradiation and one and one-half years after the last exposure for treatment of a cutaneous disease of the scalp. The dose was not known. Postmortem examination of the brain two years later showed multiple symmetric necroses, in part hemorrhagic, which occurred for the most part in the cerebral white matter, and almost exclusively in the occipitoparietal region, at the

4. Fischer, A. W., and Holfelder, H.: Lokales Amyloid im Gehirn, Deutsche Ztschr. f. Chir. **227**:475, 1930.

5. Markiewicz, T.: Ueber Spätschädigungen des menschlichen Gehirns durch Röntgenstrahlen, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:548, 1935.

place where there was greatest damage to the skin. There were a very small amount of reaction of interstitial tissue within the necroses, deposition of homogeneous substances and vascular changes of both the pial and the intracerebral blood vessels. In these 2 cases there were in common a long latent period between the onset of action of the noxa and the first appearance of symptoms, a similar pattern of clinical manifestations and an identical histopathologic picture of the brain. This evidence, together with the experimental observations on dogs,[6] indicates that the late damage from roentgen irradiation of the brain undoubtedly constitutes a histopathologic syndrome. Chukru[7] reported another case in man in which there were similar changes, the details of which, however, are not available.

The features which were common to both our cases consisted of: age and sex of the patient; mental picture; dosage and timing of irradiations; interval between exposure and death; absence of focal neurologic symptoms; slight diffuse loss of cortical nerve cells; necroses of various degrees, involving predominantly either the white or the gray substance; impregnation of a peculiar homogeneous substance on and about the blood vessels, not only in the areas of necrosis but in the preserved tissue; relative inactivity of the mesenchymal and glial tissue in organization of the defects, and mild reaction of the meninges.

The features in which the 2 cases differed were: in the first case, severe diffuse fibrosis of the meningeal and intracerebral blood vessels, and, in the second case, inclination to fatty deposits in the elastic layer, accompanied by development of foam cells in the intima and even in the lumen, and pial thrombosis. The healing power of the roentgen ulcer was definitely less in the second than in the first case.

In view of the wide extent of the lesion in the brain, it is difficult to account for the absence of symptoms in our cases. The special form of mental defect prevented the patients from making subjective complaints. Certain examinations for function of the nervous system could not be applied. In contrast to Markiewicz' finding of a definite spatial relation between the lesions in the skin and those in the brain, we were unable to reach such a conclusion. As illustrated by one of us (W. S.), Markiewicz, Mogilnitzky and Podljaschuk[8] and Alpers

6. Lyman, R. S.; Kupalov, P. S., and Scholz, W.: Effect of Roentgen Rays on the Central Nervous System, Arch. Neurol. & Psychiat. **29**:56 (Jan.) 1933. Scholz.[3]

7. Chukru, M. I.: L'action des rayons roentgen sur le cerveau, Rev. neurol. **64**:811, 1935.

8. Mogilnitzki, B. N., and Podljaschuk, L.: Röntgenstrahlen und sogenannte "hämato-enzephalische Barriere," Fortschr. a. d. Geb. d. Röntgenstrahlen **41**:66, 1930.

and Pancoast,[9] there are diffuse chronic progressive changes in the meningeal and intracerebral blood vessels in the form of fibrosis. They, together with other factors, may produce in the blood stream functional disturbances which cause the widespread fresh necroses. One of us (W. S.) and Markiewicz expressed the belief that the homogeneous substance originates from the blood vessels and may well be viewed as an antigen-antibody reaction. However, that which was seen in the first case, except in the meningeal blood vessels, may have resulted from necrosis of the walls of the vessels or of the tissue. In spite of the resemblance to Alzheimer's colloid degeneration of cerebral vessels and Spielmeyer's coagulation necrosis, these homogeneous substances can be distinguished by participation of the meningeal vessels. Both fibrosis of vessels and formation of homogeneous substances are to be regarded as changes due to roentgen irradiation. The peculiar distribution of lipoids in the lumen and intima, together with the uniform red color of the elastic membrane with scarlet red, has never been observed before in irradiated brains; it is certainly not an arteriosclerotic change, but suggests a process of hyalinization or precipitation of lipoid material, possibly due to disturbance of the function of the wall of the vessel as a barrier. The lymphocytic infiltration of the blood vessels may be symptomatic or the remnant of the *Frühreaction*. The relative inactivity of the glia in the presence of extensive necroses indicates either that the lesions are too fresh or that the glial tissue is not affected by irradiation. The latter point has already been commented on by other authors.

One of us (W. S.) has called attention to the fact that serious destruction in the brains of dogs was caused by irradiation with 8 erythema skin doses through four portals in one day, which appeared to be definitely more than the therapeutic dose for man. From our present observations, we can conclude that 4 erythema skin doses, even through six portals in three days, is enough to cause severe and extensive damage in the human brain as early as one and a half years after irradiation. The exact lowest dose which can cause damage remains to be determined.

SUMMARY

Two deteriorated young patients with schizophrenia whose heads had been irradiated with 4 erythema skin doses through six portals in three days died about one and a half years after exposure, without showing any definite focal neurologic symptoms. The brains, however, showed severe damage, which could be referred to disturbances in circulation

9. Alpers, B. J., and Pancoast, H. K.: The Effect of Irradiation of Normal and Neoplastic Brain Tissue, Am. J. Cancer **17**:7, 1933.

of the blood; they consisted of: (1) numerous and more or less extensive foci of necrosis of tissue; (2) peculiar changes, seen in other irradiated brains, in the form of severe fibrosis of vessels and deposition of peculiar homogeneous substances in the walls of the vessels and in the surrounding nerve tissue, and (3) changes in the walls of the vessels consisting of impregnation of the elastic layer with a dustlike fatty material and development of foam cells in the intima, and even in the lumen, which had a certain similarity to the process of hyalinization and which may perhaps be considered as a disturbance in the function of the vessel as a barrier due to the effect of irradiation. These late changes correspond with those described by one of us (W. S.), Markiewicz and Fischer and Holfelder. The nature and origin of these pathologic processes have been discussed briefly. Attention is called to the danger of the liberal use of roentgen irradiation of the head.

THE MEDULLOBLAST AND THE MEDULLOBLASTOMA

A STUDY OF HUMAN EMBRYOS

JOHN KERSHMAN, M.D., M.Sc.
MONTREAL, CANADA

The interest of neuropathologists in the cytogenesis of the nervous system became enhanced by the realization that gliomas contain cells resembling those seen in the brain during normal embryonic life. Yet few embryologic studies have been made to substantiate this analogy, least of all on human cytogenesis.

The term medulloblast was coined by Bailey and Cushing [1] to identify the type cell of the medulloblastoma. It was defined as a bipotential undifferentiated element analogous to the "indifferent cell" described by the embryologist Schaper.[2] The "indifferent cell" described by Schaper was an apolar element occurring ubiquitously in the growing central nervous system and capable of the dual function of neurogenesis and gliogenesis. Few subsequent embryologists have been able to identify such a cell, and its existence has come to be regarded as hypothetic (Bailey [3] and Penfield [4]).

Read at the Society of Neurological Surgeons, Montreal, Canada, June 1, 1937.

From the Montreal Neurological Institute and the Department of Neurology and Neurosurgery, McGill University.

The words "morphologic" and "embryologic," etc., are used in order to conform to the terminology which is compulsory for publication in the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. The author would prefer to use the words "morphological," "embryological," etc.

1. Bailey, P., and Cushing, H.: (*a*) Medulloblastoma Cerebelli, Arch. Neurol. & Psychiat. **14**:192 (Aug.) 1925; (*b*) Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis, Philadelphia, J. B. Lippincott Company, 1926.

2. Schaper, A.: (*a*) Die morphologische und histologische Entwicklung des Kleinhirns der Teleostiere, Anat. Anz. **9**:489, 1894; (*b*) Die frühesten Differenzierungsvorgänge im Centralnervensystems, Arch. f. Entwcklngsmechn. d. Organ. **5**:81, 1897.

3. Bailey, P.: Cellular Types in Primary Tumors of the Brain, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 953.

4. Penfield, W.: (*a*) The Classification of Gliomas and Neuroglia Cell Types, Arch. Neurol. & Psychiat. **26**:745 (Oct.) 1931; (*b*) Neuroglia, Normal and Pathological, in Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 423.

This study of human embryos and fetuses establishes that medulloblasts exist, but they occur exclusively in the cerebellum.

HISTORY AND REVIEW OF THE LITERATURE

In an analysis of a group of tumors which occur characteristically in the midline of the cerebellum, Bailey and Cushing [1a] observed that histologically these neoplasms consist of a loose, structureless mass of round or oval cells which occasionally form pseudorosettes and streams. There was little evidence of cellular differentiation, but occasionally in some areas neuroblasts, apparently derived from tumor cells, were seen, and in other areas special stains showed evidence of the formation of spongioblasts and astrocytes. They concluded, therefore, that the type cell of the tumor is an undifferentiated bipotential element capable of forming both neuroblasts and spongioblasts.

In conformity with their efforts to classify gliomas on a histogenetic basis, Bailey and Cushing tried to fit this type cell into its proper niche in the gradient of normal embryologic development. In a review of the literature, they found that Schaper, in a series of papers from 1894 to 1897, had described an "indifferent cell" the nature of which coincided with their concept of the character of the type cell of these tumors. Bailey and Cushing renamed this cell "medulloblast" and the tumor "medulloblastoma."

Schaper's first description of the indifferent cell [2a] was based on his studies of the development of the cerebellum in Teleosts (salmon and trout). During the formation of the cerebellum there occurs proliferation of the neuroepithelial cells lining the posterior tip of the roof of the fourth ventricle, and from this area cells migrate superficially over the whole outer surface of the cerebellum. As a result, the superficial, or external granular, layer of the cerebellum is formed. This is a transitory zone which disappears during the course of normal development. Schaper expressed the belief that the migrating cells forming the external granular layer are still undifferentiated and that both nerve and glia cells can originate from them; for this reason he called them "indifferent cells."

Lugaro [5] and, independently, Popoff [6] reported that by means of the Golgi method they could demonstrate the stages in the formation of

---

5. Lugaro, E.: Ueber die Histogenese der Körner der Kleinhirnrinde, Anat. Anz. **9**:710, 1894.

6. Popoff, S.: Zur Frage über die Histogenese der Kleinhirnrinde, Biol. Centralbl. **15**:745, 1895; Weiterer Beitrag zur Frage über die Histogenese der Kleinhirnrinde, ibid. **16**:462, 1896.

both nerve cells and glia cells from the elements of the external granular zone. Schaper [7] accepted this confirmation of his theories.

Cajal,[8] who was a pioneer in the use of the Golgi method, had been the first to demonstrate the growth of mature granule cells from the external granular zone, but after extensive work [9] insisted that all the glia cells of the cerebellum, as elsewhere in the nervous system, are derived from dislocated epithelial cells. He therefore rejected Schaper's hypothesis of the existence of indifferent elements in the superficial granular zone.

More recently, the ontogenesis of the cerebellum has been studied by Jacob,[10] in collaboration with Hayashi. They concluded that the cells of the external granular zone give rise to the basket cells and part of the granule cells and, while making the reservation that the question was still not definitely decided, tended to agree with Schaper that cells of the external granular zone can also give rise to glia cells and are therefore bipotential and indifferent.

In 1897, Schaper [2b] extended his histogenetic theories to include the spinal cord and brain. His [11] had expressed the belief that the wall of the medullary canal, from the time of its earliest formation, is made up of two types of cells: columnar epithelial cells and germinal cells, the latter always lying at the internal limiting membrane. The former, he concluded, produce only neuroglia; for this reason he called them primitive spongioblasts. The germinal cells, he asserted, give rise only to neuroblasts. Denying this specificity, Schaper described the columnar cells as undifferentiated neuroepithelial elements and the germinal cells as merely the same elements in mitotic division. Mitosis may result in either the formation of more neuroepithelial cells or the production of apolar indifferent cells, which as such migrate away from the ependymal region and form the first anlage of the mantle zone. He expressed the belief that the mantle zone is at first composed entirely of such indifferent cells and that these cells divide by mitosis and either produce further generations of indifferent cells or differentiate into neuroblasts and spongioblasts.

---

7. Schaper, A.: Einige kritische Bemerkungen zu Lugaro's Aufsatz: Ueber die Histogenese der Körner der Kleinhirnrinde, Anat. Anz. **10**:422, 1895.

8. Ramón y Cajal, S.: Sur les fibres nerveuses de la couche granuleuse du cervelet et sur l'évolution des éléments cérébelleux, Internat. Monatschr. f. Anat. u. Physiol. **7**:12, 1890.

9. Ramón y Cajal, S.: (*a*) Genesis de las fibres nerviosas de embryon y observaciones a la teoria catenaria, Trab. d. lab. de invest. biol. Univ. de Madrid **4**:227, 1906; (*b*) Histologie du système nerveux de l'homme et des vertébrés, Paris, A. Maloine, 1911.

10. Jacob, A.: Das Kleinhirn, in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1928, vol. 4, p. 674.

11. His, W.: Die Neuroblasten und deren Entstehung im embryonalen Mark, Arch. f. Anat. u. Entwcklngsgesch., 1889, p. 249.

From a comparative phylogenetic study, Schaper concluded that although in lower animals differentiation into neuroblasts and glia cells occurs directly from neuroepithelial cells at the ependymal level, on ascending the phylogenetic scale this becomes less true. Ultimately, in higher vertebrates, including man, more generations of indifferent cells act as intermediaries between the neuroepithelium and its differentiated products, and the latter then appear first only through the medium of indifferent cells at the level of the mantle layer. He described the indifferent cell in the ependymal zone as a pear-shaped or spindle-shaped element with an oval or elongated nucleus. Migrating outward, it reached the mantle zone and here became round, with a small amount of protoplasm and a nucleus containing a delicate chromatin structure.

His [12] later conceded that germinal cells may be neuroepithelial elements in mitosis. He denied, however, the existence of wandering indifferent cells mainly because, unlike Schaper, he did not observe mitotic figures in any layer of the nervous system except that immediately bordering the medullary canal. Paton,[13] in a study of the histogenesis of the cerebral cortex, reported that extraependymal mitoses are relatively rare but concurred with Schaper's observations regarding the presence of migratory indifferent cells. Hardesty [14] similarly described such cells but expressed the belief that some of the extraependymal mitoses seen in the developing central nervous system may belong to mesodermal connective tissue cells, which, he asserted, also participate in the formation of glia cells. The question of extraependymal mitoses will be considered more fully later.

Cajal,[9b] in an excellent summary of the whole subject, agreed with Schaper and His as to the nature of the germinal cell but concluded that neuroblasts and spongioblasts always originate directly from the cells of the ependymal zone. After extensive work with general and specific stains, he could find no evidence of wandering indifferent elements. On the other hand, Jacob and Hayashi [15] described two types of undifferentiated cells in the developing cerebral hemispheres: germinal cells and the indifferent cells of Schaper. Both these occurred ubiquitously in the developing brain and differentiated at any level;

12. His, W.: Das Princip der organbildenden Keimbezirke und die verwandschaften der Gewebe, Arch. f. Anat. u. Entwcklngsgesch., 1901, p. 307; Die Entwicklung des menschlichen Gehirns während der ersten Monate, Leipzig, S. Hirzel, 1904.

13. Paton, S.: The Histogenesis of the Cellular Elements of the Cerebral Cortex, Johns Hopkins Hosp. Rep. **9**:709, 1900.

14. Hardesty, I.: On the Development and Nature of Neuroglia, Am. J. Anat. **3**:229, 1904.

15. Jacob, A., and Hayashi, K., in Jacob, A.: Normale und pathologische Anatomie und Histologie des Grosshirns, Leipzig, Franz Deuticke, 1927, vol. 1.

these cells were said to play an important role in the formation of gyri and fissures.

It is significant that Schaper concluded that some indifferent cells remain *angeschlossen*, or "fixed," in this state till late fetal periods, and even permanently into adult life, perhaps providing the material for "regeneration processes" in the central nervous system.

Ordinary dyes demonstrate a large number of round, apparently apolar cells in the mature brain and spinal cord. Speculation by many observers as to the character of these cells led to numerous theories, and the cell was variously referred to in the early literature as Bonome's naked nucleus, Rosenthal's preameboid cell, Eisath's indifferent cell and Nissl's neuroglia cell without expansions. All were said to be analogous to the indifferent cell described by Schaper.

In 1913, Cajal,[16] by means of the gold chloride technic, demonstrated astrocytes with beautiful completeness and distinguished from them and from nerve cells a group of apolar cells which he called "the third element." Morphologically, he identified this "third element" with Schaper's indifferent cell and its aforenamed supposed analogs, but he strongly denied that it behaves as an undifferentiated germinal element. Finally, Hortega[17] clarified the situation with a further brilliant technical advance. With the silver carbonate method he demonstrated that the apolar third element consists in reality of two types of mature, well branched cells, which he named oligodendroglia and microglia cells. These elements did not in any way fit the description and function postulated by Schaper for the indifferent cells. Hortega's investigations have therefore cast doubt on the entire conception of the existence of indifferent cells or medulloblasts as a valid entity even during embryonic life.

An attempt has been made to reexamine this problem in the light of what has been learned about neurocytology since Schaper's time, and with the application of the newer methods of Cajal and Hortega that have since become available, in addition to ordinary dye stains.

---

16. Ramón y Cajal, S.: Contribución al conocimiento de la neurogliá del cerebro humano, Trab. d. lab. de invest. biol. Univ. de Madrid **11**:254, 1913; reprinted in French, ibid. **27**:389, 1932.

17. del Río Hortega, P.: (*a*) Noticia de un nuevo y fácil metodo para la coloración de la neuroglía y del tejidio conjuntivo, Trab. d. lab. de invest. biol. Univ. de Madrid **15**:1, 1918; (*b*) El tercer elemento de los centros nerviosos, Bol. Soc. españ. de biol. **9**:69, 1919; (*c*) Estudios sobre la neuroglía: La glía des ascasas radiciones (oligodendroglía), Bol. d. r. Soc. españ. d. hist. nat., January 1921, p. 63; Tercera apórtación al conoccimiento morfologico e interpretación functional de la oligodendroglía, ibid., 1928, p. 5; (*d*) Histogenesis y evolución normal; exodo y distribución regional de la microglía, ibid., 1921, p. 213.

MATERIAL AND METHODS

A large series of human embryos and fetuses was collected especially for this study.[18] Only specimens were selected which, from the history in the case and final histologic examination, were essentially normal, abortion having occurred at the time of fetal death or the embryo having been delivered by operation. In all cases the Wassermann reactions of the blood of the fetus or mother were negative, and congenital or transmitted disease or the presence of toxic changes of pregnancy and other conditions which might cause pathologic changes in the nervous system was ruled out.

Twenty-two specimens, ranging in prenatal age from 8 to 29 weeks, met these requirements. The age was estimated according to the charts of Streeter [19] and the history in the case.

In all the specimens selected, fixation was carried out either immediately or within two hours. About half were first fixed in a solution of formaldehyde and ammonium bromide.[20] One embryo, aged 11 weeks, was fixed immediately in the mixture of solution of formaldehyde and bromalin of Bielschowsky [21] and stained by the methods recently outlined by him. The brain and spinal cord of a specimen (aged 27 weeks), obtained from Dr. G. L. Streeter, of the Carnegie Institute of Embryology, were fixed in Bouin's solution for four days and then stored in 70 per cent alcohol. The others were fixed in a dilute solution of formaldehyde U. S. P. (1:10). In most cases the fixative was injected before removal. After removal of the brain and spinal cord, blocks were cut and transferred to a series of fixatives so as to make possible a complete histologic study by metallic methods and dye stains. Frontal sections of the hemispheres, sagittal sections of the brain stem and cerebellum and transverse and longitudinal sections of the spinal cord were used.

In addition to these specimens, a number of brains from infants ranging in age from birth to 17 months were examined. These children had died of an acute infection (usually of the respiratory tract) without direct involvement of the central nervous system. Postmortem examination was made in from one to twelve hours, and the tissues were fixed in a dilute solution of formaldehyde U. S. P. (1:10).

The metallic methods of Cajal and Hortega (outlined by Penfield and Cone [22]), as they are carried out routinely at the Montreal Neurological Institute, were used. It soon became obvious that embryonic cells do not have the same staining reactions to silver and gold as adult cells. Moreover, the softness of the tissue necessitates the use of thicker frozen sections and more careful handling. Various

---

18. Dr. W. H. Chase, pathologist at the Royal Victoria and the Women's General Hospital, presented many of the specimens.

19. Streeter, G.: Weight, Sitting Height, Head Size, Foot Length and Menstrual Age of the Human Embryo, Contrib. Embryol. **11**:1, 1920.

20. The fixative consists of solution of formaldehyde, 15 cc.; ammonium bromide, 6 Gm., and distilled water, to make 100 cc.

21. Bielschowsky, M.: Neue Silberimprägnationsversuche zur Darstellung der Neuroglia und deren Ergebnisse, Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:253, 1931.

22. Penfield, W., and Cone, W. V.: Neuroglia and Microglia (The Metallic Methods), in McClung, C. E.: Handbook of Microscopical Technique, New York, Paul B. Hoeber, Inc., 1929, pp. 359-388.

modifications suggested by Hortega,[17b] Hortega and Asúa,[23] Globus[24] and Penfield and Cone,[22] as well as others, were used.

In general, for the staining of spongioblasts in their various forms and for the staining of neuroblasts, especially in the cerebral hemispheres, it was found that formaldehyde-fixed material impregnated by the method of Penfield[25] for combined staining of oligodendroglia and microglia cells was best. For complete staining, prolonged immersion in a solution of silver carbonate was advisable until the sections were light brown. The medulloblasts in the cerebellum were stained in this way. Better results were sometimes obtained by warming the sections to about 60 C. in silver carbonate (to which was added six drops each of pyridine and 95 per cent alcohol) until they were amber. An undiluted solution of silver carbonate was found to be better than weaker solutions. Prolonged fixation in formaldehyde (even for years) still permitted good staining by this method.

The material fixed in Bouin's solution and 70 per cent alcohol was later placed in a dilute solution of formaldehyde U. S. P. (1:10) for about eight or ten days and then cut, and the sections were washed in 70 per cent alcohol for one or two minutes. They were then stained by the same method (left in ammonia overnight, etc.), with excellent results. The methods of Cajal and Bielschowsky for neurofibrils and various modifications of these procedures were carried out. Methods employing dye stains such as hematoxylin and eosin, Van Gieson's phosphotungstic acid hematoxylin and the Nissl and Weigert-Pal technics, were also used in this study.

OBSERVATIONS

Because of its undifferentiated nature, the medulloblast is difficult to identify by any positive characteristics. Based on Schaper's original definition, which was adopted by Bailey, there are, however, certain biologic criteria by which its existence may be substantiated.

It will be recalled that, according to Schaper, the youngest neuroblasts and spongioblasts appear first only in the mantle zone, which is formed in its earliest stages exclusively of indifferent cells. The identification of the site of differentiation therefore assumes great importance in this study. If there is an apolar bipotential cell dispersed through the growing central nervous system, it should be possible to identify the extraependymal mitoses by which it multiplies and differentiates, and it should be demonstrated that both newly formed neuroblasts and spongioblasts resulting from such differentiation appear first in regions far removed from the ependymal zone.

The spinal cord, the cerebrum and the cerebellum will be considered separately.

Spinal Cord.—The spinal cord of a 3.4 mm. human embryo (fig. 1) was composed of a dense, multicellular epithelium in which almost all the constituent

23. del Río Hortega, P., and Jiménéz de Asúa, F.: Sobre la fagcoitosis en los tumores y en otros proceosos pathológicos, Arch. cardiol. y hemat. **2**:161, 1921.

24. Globus, J. H.: The Cajal and Hortega Glia Staining Methods, Arch. Neurol. & Psychiat. **18**:263 (Aug.) 1927.

25. Penfield, W.: Method of Staining Oligodendroglia and Microglia (Combined Method), Am. J. Path. **4**:153, 1928.

nuclei followed the same definite alinement. Only two zones were present, a thick ependymal zone and a thin peripheral marginal zone. With the hematoxylin and eosin stain no cellular differentiation could be observed; almost all the cells seemed to be uniformly epithelial in character. Mitotic division was seen only beneath the internal limiting membrane. The marginal zone was free from nuclei. At the periphery of the anterior part of the neural wall, however, there were several round and oval nuclei (fig. 1-*M*) which did not conform to the general parallel alinement. This change in the orientation of certain cells demonstrates the earliest

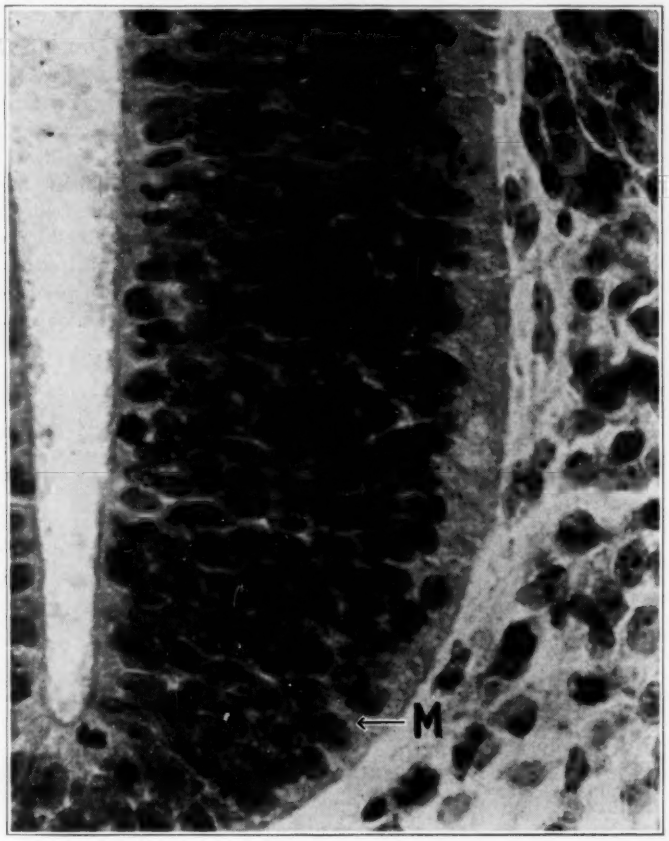


Fig. 1.—Photomicrograph of the anterior segment of the spinal cord in an embryo 3.4 mm. in length. *M* indicates oval and round nuclei of cells forming the first evidence of the mantle zone. Hematoxylin and eosin stain (Carnegie collection, no. 6097, by permission of Dr. G. L. Streeter).

formation of the mantle zone. Without special stains, which were not available in this specimen, it was impossible to identify accurately the character of these cells. Progressive growth led to the accumulation of such cells in the periphery of the ependymal layer, forming a wide mantle zone.

The first specimen in which specific stains could be used was a 25 mm. embryo, aged 8 weeks (fig. 2). At this age the ependymal region in the basal half of the

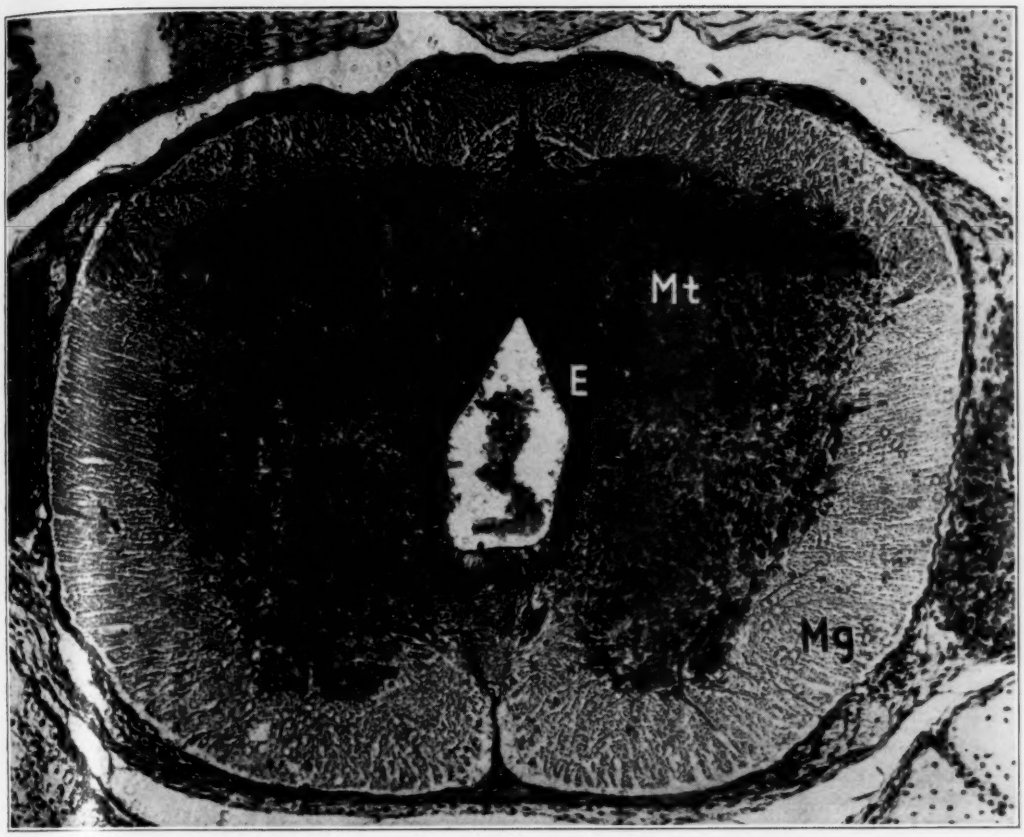


Fig. 2.—Photomicrograph of the spinal cord of an 8 week embryo. *E* indicates the ependymal zone; *Mt*, the mantle zone, and *Mg*, the marginal zone. Hematoxylin and eosin stain.

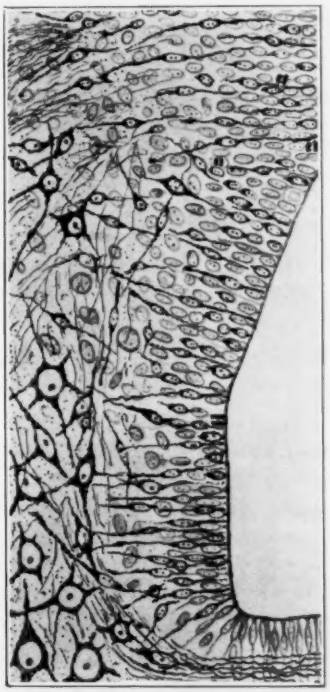


Fig. 3.—Composite drawing of the spinal cord of an 8 week embryo. The youngest neuroblasts are apolar cells with argentophilic neurofibrillar substance, and they are in the ependymal zone. The more mature types are peripheral. Bielschowsky stain.

spinal cord was fairly well delimited from the mantle zone. In the alar, or posterior, half the distinction was much less sharp: The ependymal and the mantle zone merged more imperceptibly, indicating a continuous flow of cells from the former to the latter.

Specific stains for neurofibrils demonstrated that the youngest neuroblasts were apolar cells characterized by the presence of an argentophilic fibrilogenous zone

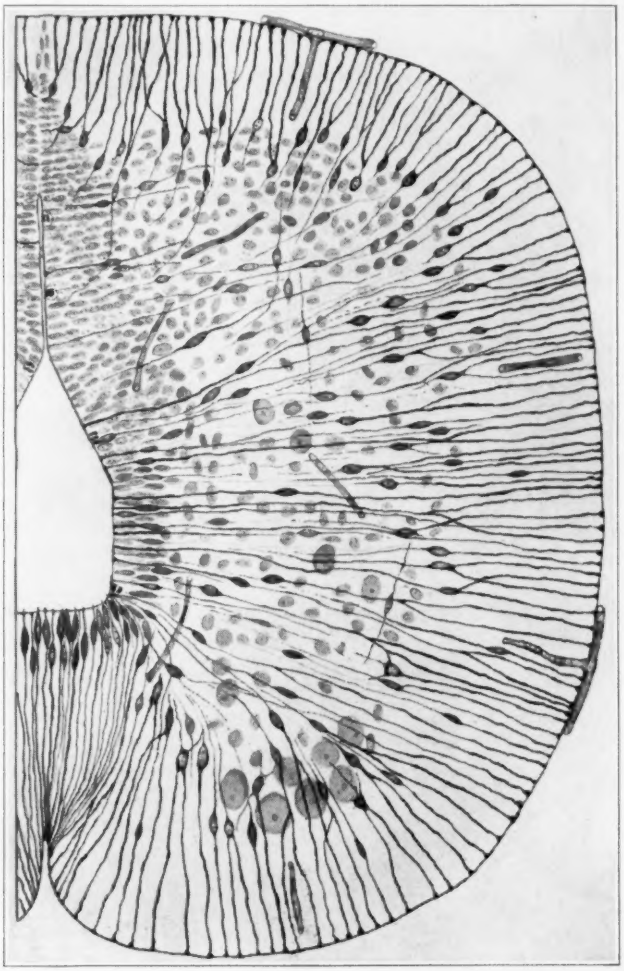


Fig. 4.—Composite drawing of the spinal cord of an 8 week embryo, showing distribution and character of spongioblasts. Silver carbonate stain.

of Held (fig. 3). These cells occurred in the ependymal region; anteriorly they were seen at the internal limiting membrane, and posteriorly, where the ependymal zone was wider, they also occasionally occurred among the deeper cells of this region. Radiating from the ependymal zone were bipolar cells containing neurofibrillar material; these seemed to be older than the apolar neuroblasts and were probably derived from the migration of the latter. Some of the bipolar cells had

lost their internal expansions and were becoming unipolar. At this stage they had also lost their ependymal alinement and were in the mantle zone, appearing there as unipolar neuroblasts. More peripherally in the mantle zone there were neuroblasts with secondary bipolar and multipolar expansions, simulating mature nerve cells (fig. 3). It was evident, therefore, that in the presence of well formed

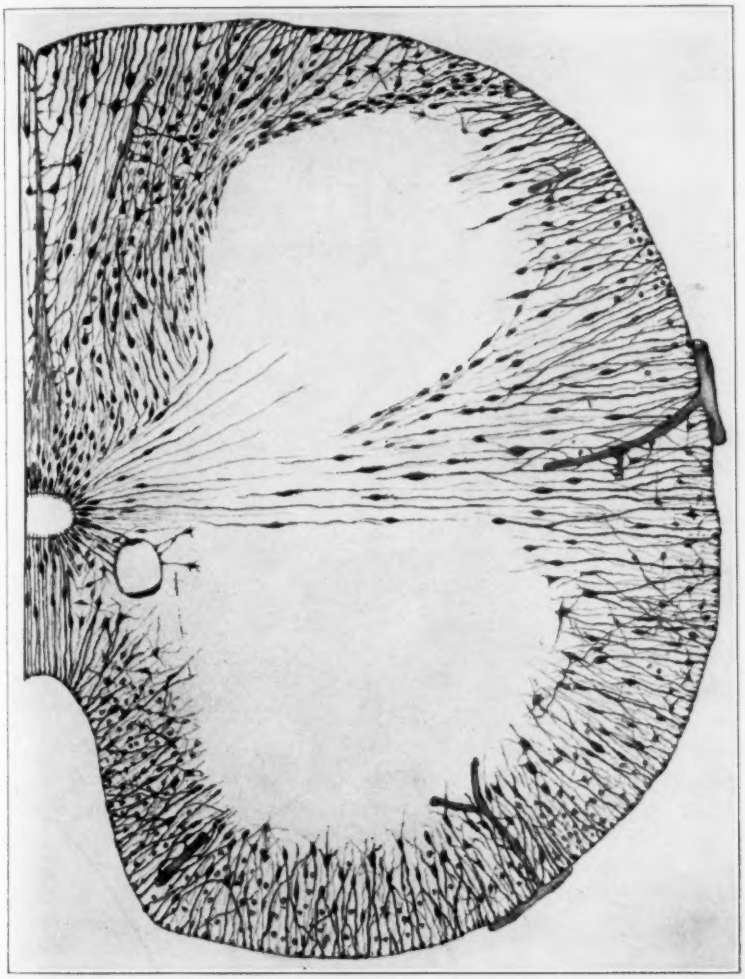


Fig. 5.—Composite drawing of the spinal cord of a 16 week embryo, showing distribution and character of spongioblasts. Apolar cells are appearing, especially in the tract zones: the tractus cuneatus and the anterior and anteromedial ground bundles. Silver carbonate stain.

nerve cells of the anterior horn more neuroblasts were still being formed, but the youngest stages of apolar cells constantly occurred in the ependymal zone.

Figure 4 shows the appearance of spongioblasts at the same age (8 weeks). In human embryos, similar to what Cajal and others observed in chicks, the dif-

ferentiation and growth of neuroblasts preceded the maturation of spongioblasts. The supportive elements at this age were elongated polar spongioblasts with expansions reaching toward the internal and external limiting membranes. Occasionally these cells showed evidence of further development by loss of their internal expansions, especially some in which the cell bodies were in or near the marginal zone. At this age mitoses occurred almost exclusively at the internal limiting membrane, except posteriorly, where occasionally there were dividing cells in the deeper layers of the ependymal region.

At about the 11 week stage there occurred a definite formation of migratory apolar cells. They were first seen to best advantage in the posterior part of the spinal cord, where the long tracts were now being laid down, but they also occurred in other tract areas (fig. 5). These apolar cells originated in two ways. Some appeared to migrate directly as such from the ependymal zone, but, in

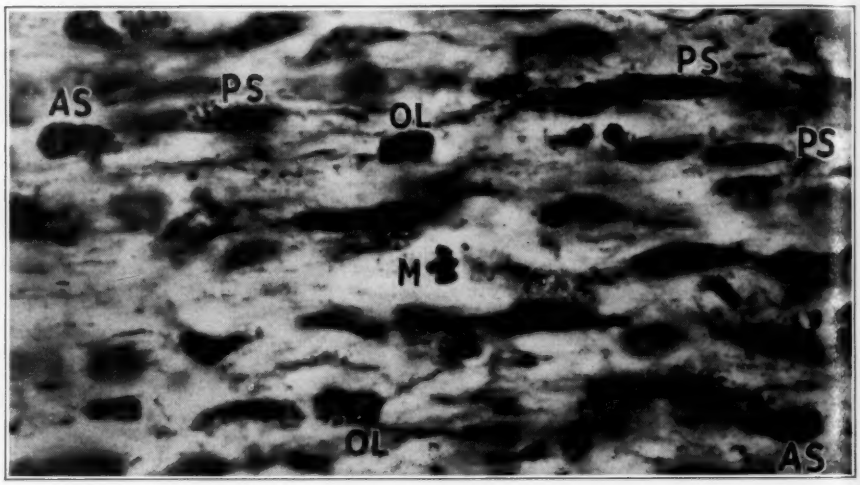


Fig. 6.—Photomicrograph of a longitudinal section of the spinal cord of a 16 week embryo, in the region of the posterior columns. *AS* indicates an apolar spongioblast; *M*, a mitotic figure in a spongioblast; *Ol*, an oligodendroblast, and *PS*, a polar spongioblast. Silver carbonate stain.

contrast to the apolar neuroblasts, neurofibrils were never stained within them. Others were formed from the division of polar spongioblasts (fig. 6).

At the same time that these apolar cells appeared, increasing numbers of extraependymal mitoses occurred; most of them were seen in the marginal zone, where simultaneously tracts were being formed and glia cells were increasing rapidly. The number of extraependymal mitoses diminished again from about the fifth month.

When completely stained with silver carbonate, it became clear that these round apolar cells had a small nipple of protoplasm at one or two sides. When their future course of development was traced with silver carbonate and other stains, it was apparent that they gave rise to oligodendroblasts. Figure 6 shows the posterior columns of the spinal cord at the 16 week stage and illustrates the

formation of oligodendroblasts from apolar cells, while mitotic division is seen in these cells and in polar spongioblasts. The formation of oligodendroblasts from apolar cells and their accumulation seem to occur just before myelination. At the 20 week stage, in a comparison of the oligodendroblast content of the tractus

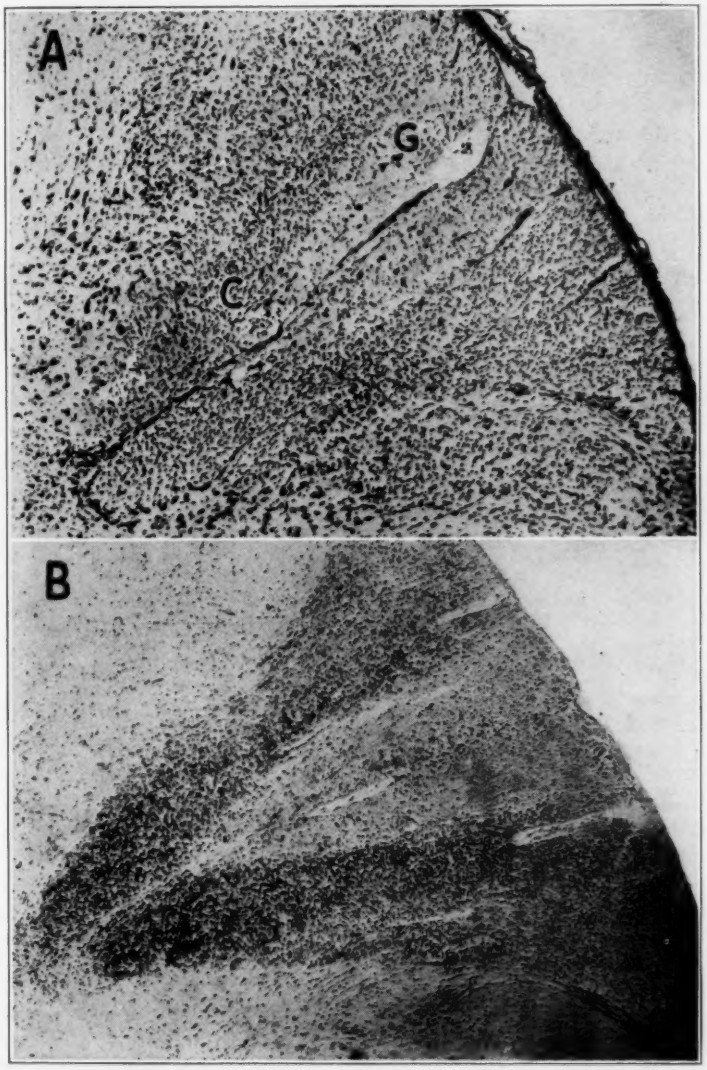


Fig. 7.—Spinal cord of a 20 week embryo. *A* shows the distribution of oligodendroblasts (silver carbonate stain), and *B*, the distribution of myelin (Weigert-Pal stain). Both oligodendroblasts and myelin are more profuse in the tractus cuneatus (*C*) than in the tractus gracilis (*G*).

cuneatus with that of the tractus gracilis (fig. 7), it was observed that these cells were more numerous in the tractus cuneatus, and Weigert-Pal stains showed that myelin was distributed with the same relative density.

Occasionally, after the apolar cells had formed oligodendroblasts some of the latter formed astrocytes, as was described by Penfield.[26] But there was no evidence that these apolar cells acquire neurofibrils, to give rise to neuroblasts. It is obvious, therefore, that these apolar cells are migratory spongioblasts.

Figure 8 summarizes the cytogenesis of the spinal cord. Since new neuroblasts all seem to rise in the ependymal region and the apolar migratory cells are apolar spongioblasts, there is no evidence of the existence of Schaper's indifferent cells.

Cerebrum.—Development of the wall of the cerebral hemispheres began with the same fundamental plan as that of the spinal cord, by formation of ependymal, mantle and marginal zones. However, where the mantle zone adjoined the ependymal region a dense layer of transitional cells accumulated, which is referred to as the subependymal zone. Shortly after, at the periphery of the mantle zone, a

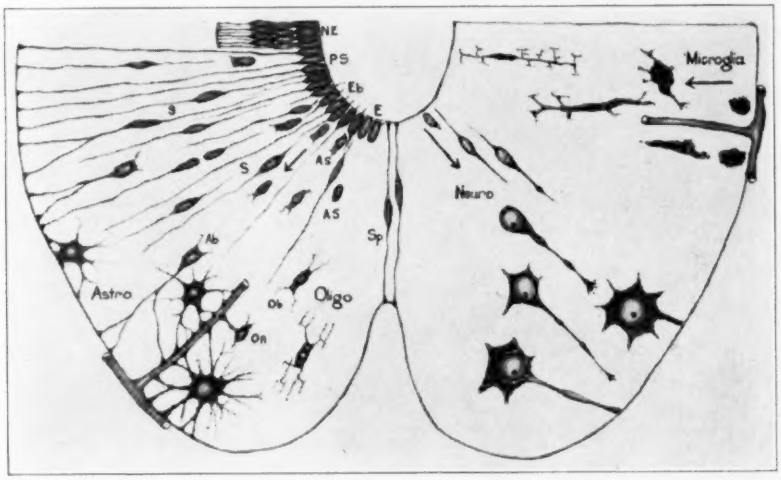


Fig. 8.—Diagram illustrating cytogenesis in the spinal cord. *Ab* indicates an astroblast; *AS,* apolar spongioblasts; *Astro,* astrocytes; *E,* ependyman; *Eb,* ependymoblasts; *NE,* neuroepithelium; *Neuro,* neuroblastic cells; *OA,* an oligodendroblast acquiring a vascular foot to become an astroblast; *Ob,* an oligodendroblast; *PS,* primitive spongioblasts; *S,* spongioblasts (polar forms), and *Sp,* supportive spongioblasts.

The neuroepithelial cells give rise to neuroblasts and spongioblasts. After neuroblast formation has ceased, the cells remaining in the ependymal zone may be called primitive spongioblasts; gradually, the remaining cells become ependymoblasts, and finally ependyma. In the meantime, from the ependymal region there is a constant discharge of polar and apolar spongioblasts, which develop into astrocytes and oligodendroglia cells. In the median raphe of the spinal cord supportive spongioblasts persist as the adult mature cells of this region. Microglia cells, in the forms shown in the upper right corner, migrate into the spinal cord from the mesenchymal cells.

---

26. Penfield, W.: Neuroglia and Microglia: The Interstitial Tissues of the Central Nervous System, in Cowdry, E. V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1928, vol. 2, p. 1032.

compact lamination of cells occurred, forming the primitive cortical zone. The part of the mantle zone between the subependymal and the cortical layer is referred to as the intermediary zone (fig. 9).

In locating the site of neuroblast formation in the hemispheral wall it was found that, in contrast to the spinal cord, the demonstration of intracellular neurofibrils could not be accepted as the earliest evidence of differentiation of neuroblasts. The silver carbonate method of Penfield distinguished definite neuroblasts long before intracellular neurofibrils were demonstrable by any of the Cajal or

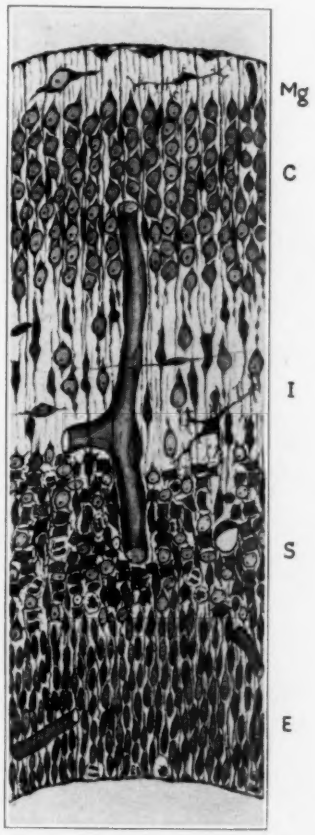


Fig. 9.—Composite drawing of the hemispheral wall of an 11 week embryo. *C* indicates the cortical zone; *E*, the ependymal zone; *I*, the intermediary zone; *Mg*, the marginal zone, and *S*, the subependymal zone. Silver carbonate (Bielschowsky's bromalin method).

Bielschowsky stains or their modifications. This tardy appearance of neurofibrils in cerebral neuroblasts has also been reported by Brodmann,[27] Gierlich,[28] Cajal [9b] and Tello.[29]

27. Brodmann, K.: Demonstration von Fibrillenpräparaten und Histogenese des Centralnervensystems, Neurol. Centralbl. **24**:648, 1905; Bemerkungen über die Fibrillogenie und ihre Beziehungen zur Myelogenie, mit besonderer Berücksichtigung des Cortex cerebri, ibid. **26**:338, 1907.

(Footnotes continued on next page)

With the silver carbonate method, the following stages in the differentiation of neuroblasts could be defined: 1. The earliest recognizable neuroblasts in the hemispheral wall were apolar cells. They possessed a spherical nucleus, a relatively thick nuclear membrane and a small, irregular mantle of coarse, granular protoplasm. These apolar forms invariably occurred in the subependymal zone (figs. 9 and 10*A*).

2. The intranuclear chromatin of these cells then tended to disperse and form from two to four larger granules, which were then contained in a pale vesicular nucleus.

3. These larger granules merged to form a single nucleolus. The nucleus remained spherical, with a firm nuclear membrane, and the protoplasm of the cell body was coarsely granular, elongated and polarized. This form was characteristic of the intermediary region (figs. 9 and 10*c*).

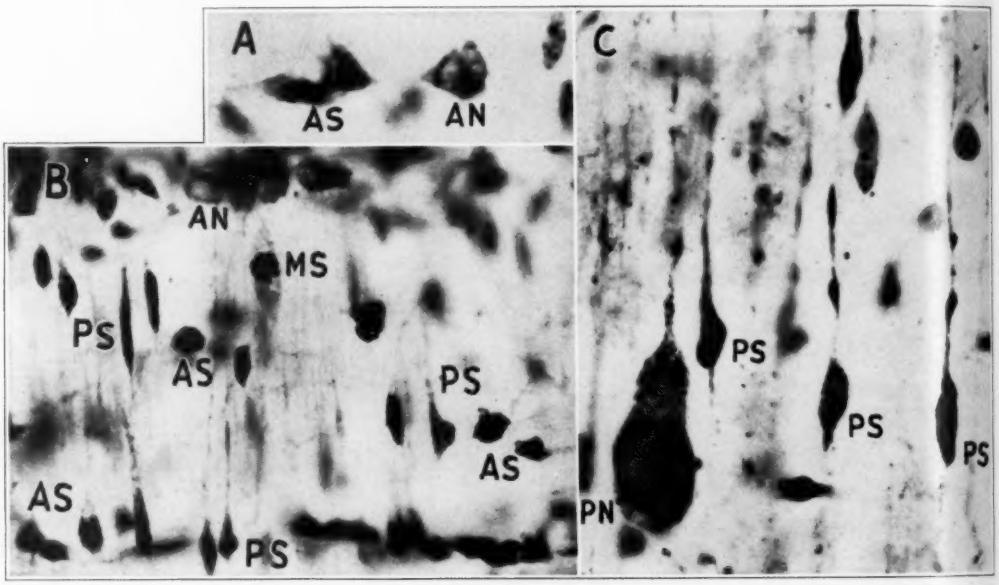


Fig. 10.—Hemispheral wall of a 16 week embryo. *A* shows the subependymal zone; *B*, the subependymal zone, in which transition forms from apolar to polar spongioblasts can be seen, and *C*, the intermediary zone. *AN* indicates apolar neuroblasts; *AS*, apolar spongioblasts; *MS*, a spongioblast in mitotic division; *PN*, polar neuroblasts, and *PS*, polar spongioblasts.

4. Intracellular neurofibrils became demonstrable. This occurred first in the cortical plate after from the 18 to the 20 week stage, the exact time varying in different locations.

---

28. Gierlich, N.: Ueber die Entwicklung der Neurofibrillen in der Pyramidenbahn des Menschen, Deutsche Ztschr. f. Nervenh. **32**:97, 1906.

29. Tello, J. F.: Évolution des formations neurofibrillaires dans l'écorce cérébrale du foetus de souris blanche depuis les 15 mm. jusqu'à la naissance, Trav. du lab. de recherches biol. de l'Univ. de Madrid **30**:477, 1935.

5. Nissl substance appeared, usually shortly before birth but also varying widely in different locations and cell types.

The first neuroblasts to accumulate in the cortical plate were, naturally, immature cells, but they passed through the same phases in development as those already outlined.

In the subependymal zone, in addition to the apolar neuroblasts, there were a large number of apolar cells which also stained completely with silver carbonate (fig. 9). These were more irregular, and the nucleus was oval, pear shaped or roughly quadrilateral. The nuclei were slightly smaller than those of the neuroblasts and were more densely granular and deeply stained (fig. 10*A*). The cytoplasm was thin, uneven and variable in amount and was often collected at one or two parts of the cell, forming a small nipple. There were innumerable morphologic variations of these apolar forms by which they gradually merged into typical polar spongioblasts in and beyond the subependymal zone (figs. 9 and 10*B*). The countless transition forms demonstrated that these apolar cells are direct antecedents of polar spongioblasts and are themselves apolar spongioblasts.

While the subependymal region abounded with apolar forms, the intermediary zone was composed entirely of polar cells, both neuroblasts and spongioblasts (figs. 9 and 10*C*), and differentiation between them was easily made on the basis of morphologic criteria. No apolar elements occurred in the intermediary or the cortical region until after 7 months. Then, as a prelude to myelination, oligodendroblasts began to appear. They were derived from apolar spongioblasts, and their development was like that of similar cells in the spinal cord.

The occurrence and distribution of extraependymal mitoses in the hemispheral wall were important. By far the greatest number occurred in the subependymal region. They gradually increased here up to about the fourth month, when they outnumbered those seen in the ependymal zone itself. Then they slowly diminished and disappeared. Many mitoses were seen in the inner half of the intermediary zone, but only rarely in the outer half and almost never in the cortical zone.

The ependymal region during the development of the cerebrum was a much thicker bed of cells than that in the spinal cord, and for a long time no differentiation was visible within it. As long as this was so, mitoses here served only to reproduce undifferentiated neuroepithelial elements. The earliest forms of neuroblasts and spongioblasts were visible in the subependymal region, and numerous mitoses occurred here in apolar cells the exact nature of which during division had necessarily to remain uncertain. Most dividing cells became round and lost their differentiating qualities during the phase of actual splitting. But a great number were observed in varying stages between the prophase and the telophase which retained their protoplasmic expansions. Silver carbonate stains demonstrated both the chromosomes of the dividing cell and the protoplasm (fig. 10*B*, *MS*). By this method, cells which could be identified as spongioblasts were seen in mitotic division (fig. 11*A*). In tract areas, such as the corpus callosum and the internal capsule, spongioblasts retaining remarkably long protoplasmic expansions were observed in various stages of mitosis.

Some of the dividing cells in the subependymal zone were somewhat larger than spongioblasts; the nucleus was more spherical and the cytoplasm more voluminous and granular. On morphologic criteria they were identified as neuroblasts undergoing mitosis (fig. 11*B*). This tendency of new-formed neuroblasts in the subependymal zone to multiply by mitosis may explain the absence of intracellular neurofibrils. The latter is a highly differentiated structure the presence

of which would probably preclude division. Mitosis in neuroblasts has also been reported by Hamilton,[30] Hatai [31] and Ariëns Kappers.[32]

The most intense cellular differentiation in the hemispheral wall occurred up to the fifth month; after this there was a gradual decrease in the formation of fresh neuroblasts. It is significant that neither apolar cells nor mitoses were seen in the outer half of the intermediary zone and the cortical region even during this period. It seems clear that newly differentiated neuroblasts or spongioblasts were not formed in situ in the intermediary or the cortical region. These zones were populated exclusively by cells which had migrated outward either as neuroblasts or as spongioblasts from periventricular levels where differentiation and proliferation occur. There was therefore neither direct nor indirect evidence that medulloblasts or migratory indifferent cells exist in the hemispheral wall.

The site of the caudate nucleus deserves special mention. Here the ependymal zone of cells underwent tremendous thickening, forming a uniformly dense sheet

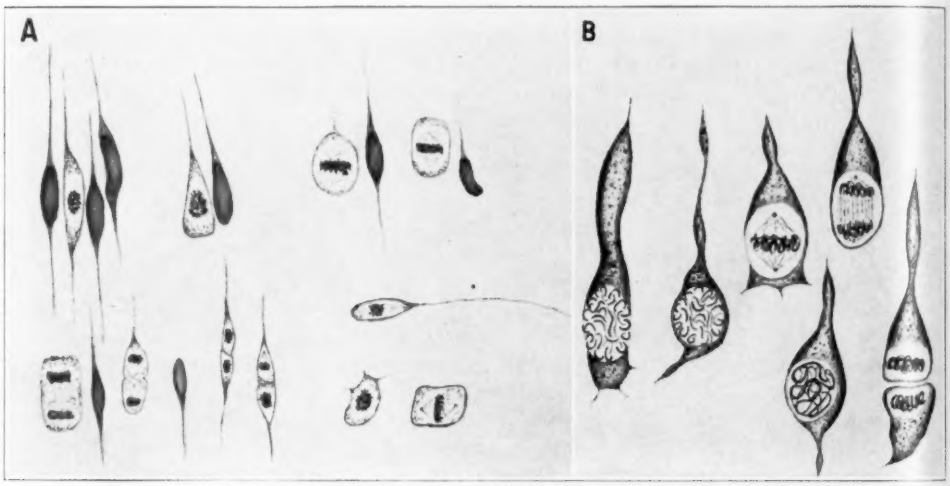


Fig. 11.—Mitotic figures in the subependymal and the inner part of the intermediary zone, drawn from silver carbonate stains of the hemispheral wall of a 16 week embryo. *A* shows spongioblast forms, and *B*, neuroblast forms, in mitosis.

of closely packed elements. This area, known in the German literature as the *Ganglienhügel,* was the germinal bed for the formation of the basal ganglia. Similar histologic changes occurred earlier, during the formation of the thalamus. Continued proliferation caused the ependymal cells to be pushed away from the ventricular border and to lose their columnar appearance, assuming instead an

30. Hamilton, A.: Division of Differentiated Cells of the Central Nervous System of the White Rat, J. Comp. Neurol. **11**:297, 1901.

31. Hatai, S.: Mitosis in the Nerve Cells of the Cerebellar Cortex of the Foetal Cat, J. Comp. Neurol. **11**:277, 1901.

32. Ariëns Kappers, C. U.: The Principles of Development of the Nervous System, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 1, p. 43.

irregular shape. Sometimes the cells grew in streams surrounding a blood vessel, and in cross section this sometimes suggested rosette formation.

Differentiation was visible only at the periphery of this ependymal mass, where pale vesicular neuroblasts and dense irregular spongioblasts could be distinguished. With growth the undifferentiated ependymal region progressively narrowed, so that at from 7 to 8 months there remained only bands of periventricular cells, often arranged around blood vessels. This appearance has been described by numerous observers; normally, these undifferentiated cells soon disappear (Schwarz, Goolker and Globus [33]). Pathologically, nests of these cells may persist for a long time postnatally (Alpers,[34] Ferraro and Barrera [35]).

There is no evidence that these undifferentiated periventricular cells migrate as such into the periphery to form medulloblasts. For example, in the cellular bridges passing from the site of the caudate nucleus across the internal capsule and supplying cells to the growing putamen, all the elements were recognizable as either neuroblasts or spongioblasts of the same polar type as that seen in the intermediary zone elsewhere.

One other phenomenon requires description. At about the fifth or sixth month (varying in different areas) the ependymal zone narrowed and lost its multilayered structure. By this time (with wide local variations) neuroblast formation was subsiding, and the ependymal zone consisted of "primitive spongioblasts" which soon become ependymoblasts. From that time, large oval and round nuclei made their appearance in the subependymal region and more peripherally. Rydberg [36] recently described them in newborn infants and fetuses as "naked nuclei." When they were completely stained with silver carbonate, however, a large variable protoplasmic cell body surrounding the nucleus could be demonstrated (fig. 12 *A*).

In migrating outward, most of these cells acquired long internal and external expansions (fig. 12 *B*). Ultimately, they all acquired vascular feet, to form astroblasts. Their behavior was similar to that of the large polar spongioblasts occurring in great numbers at this time, which were known as "dislocated epithelial" cells by earlier investigators. These so-called naked nuclei of Rydberg are therefore spongioblast cells. They are best studied in such regions as the corpus callosum, where the ependymal zone stops producing neuroblasts at a very early age.

In conclusion, therefore, it may be said that there is no evidence of a ubiquitous bipotential element, such as the medulloblast or Schaper's indifferent cell, in the hemispheral wall.

Cerebellum.—Because of the peculiarly complex structure of the cerebellar cortex, a few words are necessary to outline the normal histologic structure. The neuronal components are basket cells and star cells in the molecular layer. Below are the Purkinje cells, and beneath them, the granule cells. Between the last two regions there are Golgi nerve cells. The neuroglia cells include oligodendrocytes, which are diffusely present in all the layers, and protoplasmic astrocytes, which

---

33. Schwarz, H.; Goolker, P., and Globus, J. H.: The Normal Histology of Infant's Brains, Am. J. Dis. Child. **43**:889 (April) 1932.

34. Alpers, B. J.: Diffuse Progressive Degeneration of the Gray Matter of the Cerebrum, Arch. Neurol. & Psychiat. **25**:469 (March) 1931.

35. Ferraro, A., and Barrera, S. E.: Megalo-Myelo-Encephaly, Am. J. Psychiat. **92**:509, 1935.

36. Rydberg, E.: Cerebral Injury in Newborn Children Consequent on Birth Trauma, with an Inquiry into the Normal and Pathological Anatomy of the Neuroglia, Acta. path. et microbiol. Scandinav., 1932, supp. 10, pp. 1-247.

occur in the granule cell layer and are similar to those seen elsewhere in the gray matter of the brain except that here, from the more peripheral cells, expansions often pass to the molecular layer and reach the external surface, to form subpial foot plates.

In addition, two types of astrocytes occur specifically in the cerebellar cortex. One is the Golgi epithelial cell, the cell body of which lies in or just above the Purkinje cell layer. The expansions of this cell are known as Bergmann fibers; usually they pass straight upward to end beneath the pia, though occasionally they end on a blood vessel. The second type was described by Fañanás, in 1916.[37] Its cell body usually lies in the lower part of the molecular zone, and there is usually one, but sometimes two or three, expansions which seem to end in the molecular zone (Jacob [10]). These expansions have characteristic short feathery branches, and the cells are often referred to as the "feather cells of Fañanás." Penfield [4b] expressed the belief that these two special astrocytes are similar, the Golgi epithelial cell being the fibrous subpial astrocyte and the Fañanás cell the

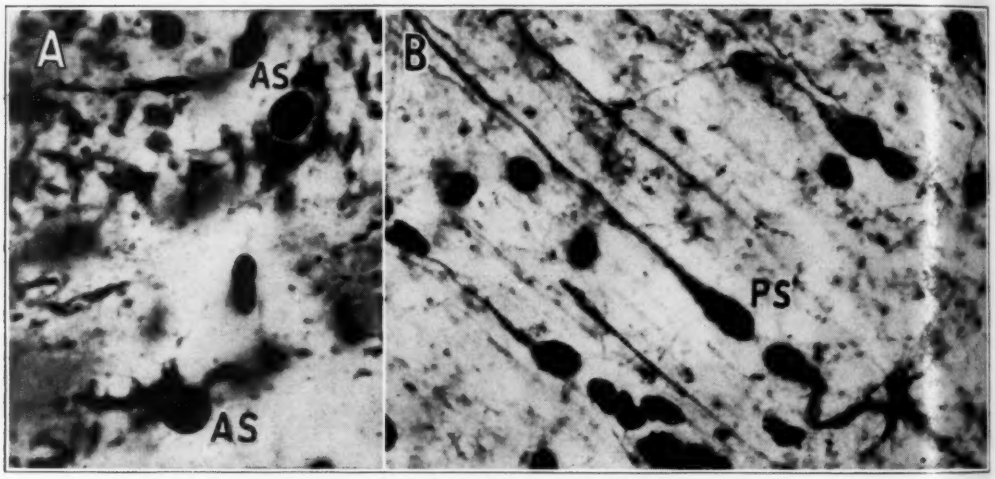


Fig. 12.—Photomicrograph, the subependymal zone in a 27 week embryo. *A* shows large apolar spongioblasts (*AS*) and *B*, the large "dislocated epithelial" type of polar spongioblast (*PS*). The apolar forms also give rise to the large polar cells. Silver corbonate stain.

protoplasmic subpial astrocyte. Microglia cells are also present in the cerebellum, but will not be considered here.

Embryologically, it was observed that during the development of the cerebellum, from about the third month, an external granular zone was formed. This originated from the posterior tip of the roof of the fourth ventricle. The neuroepithelial cells of this region proliferated and formed a dense cellular nest, and from this nest cells migrated forward over the entire external surface of the cerebellum, forming a sheet of cells which became the external granular zone (fig. 13). This zone persisted almost to the end of the first year of postnatal life, gradually disappearing during the second six months. The cells of this zone

37. Fañanás, J. R.: Contribución al estudio de la neurogliá del cerebelo, Trab. d. lab. de invest. biol. Univ. de Madrid **14**:163, 1916.

during embryonic life were closely packed together and, as a result, varied in shape. In the main, however, they were somewhat round or oval, though sometimes flattened; they had a densely granular nucleus, and in successful silver carbonate stains a fine short expansion, usually lying parallel to the surface, could be seen at one or both ends (fig. 17 *Med*). Mitotic figures were frequent among these cells.

From the time of its earliest formation there was a constant flow of cells from the external granular zone, which migrated inward to the substance of the cere-

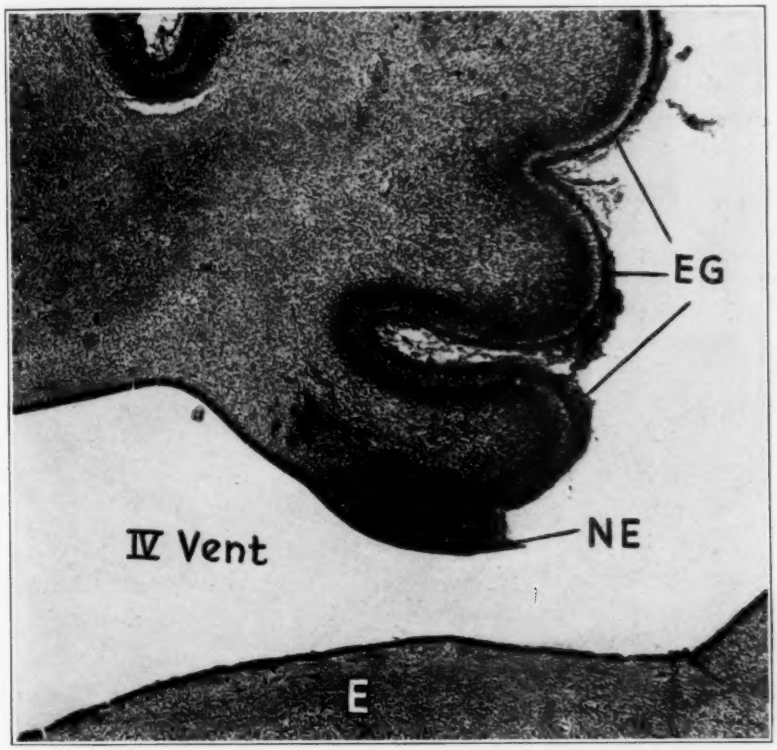


Fig. 13.—Photomicrograph of the cerebellum and fourth ventricle of a 16 week embryo. The posterior tip of the roof of the fourth ventricle consists of a dense mass of proliferating cells. The superficial, or external granular, zone (*EG*) is a direct continuation of it. *NE* indicates neuroepithelial cells. Silver carbonate stain.

bellum, so that ultimately the zone itself disappeared. The character of the cells emerging in this way varied at different ages. Until about the time of birth the migrating cells consisted almost exclusively of round or oval elements (fig. 14), which culminated in the formation of mature internal granule cells. The developing stages could be demonstrated with silver carbonate stains (fig. 17 *G*) and resembled all the phases so well described by Cajal.[9b] These cells could be traced through the Purkinje zone, leaving behind an expansion in the molecular layer which formed the axon of the granule cell.

Just before birth the Purkinje cells began to elaborate their characteristic "candelabra" expansions, but there was as yet no evidence of the Golgi-Bergmann and Fañanás cells.

From birth (fig. 15) it was evident that two distinct cell types emanated from the external granular layer (in which mitosis was still taking place). One of these was a spherical, sometimes flattened, darkly staining cell, similar to the immature granule cell, with expansions parallel to the outer surface (fig. 15 *B*). These could be traced to lower levels of the molecular zone; they gradually developed into basket cells (fig. 17 *B*). The other type was the more important from the standpoint of this study. This was a cell which, from the time of its earliest formation, had an elongated, spindle-shaped nucleus and a cell body the

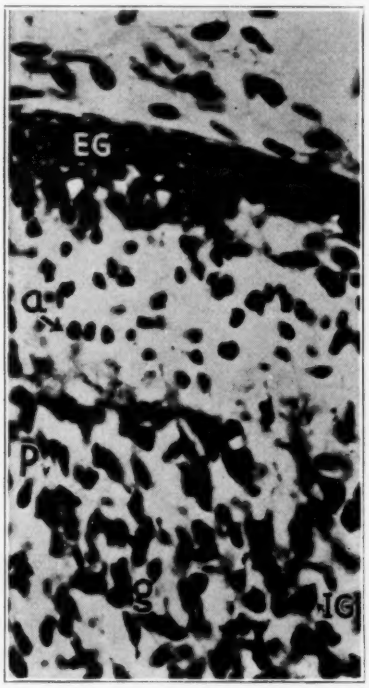


Fig. 14.—Cerebellar cortex of a 4 month embryo. The cells derived from the external granular zone (*EG*) at this age are round and oval cells (*a*) which migrate through the Purkinje cell zone (*P*) to form granule cells (*g*) in the internal granular zone (*IG*).

long axis of which was perpendicular to the surface (fig. 15 *S*). Its shape and direction immediately distinguished it from the elements previously described. The cell body could be traced inward by progressive stages, forming as it proceeded inner and outer polarized expansions, which were also at right angles to the external surface. These cells did not migrate through the Purkinje cell zone, but came to rest at or just above it. In so doing the cell body became rounded and assumed a pear-shaped or oval outline. When this happened (fig. 16 *F*) it became evident that these elements were gradually transformed into Golgi-Bergmann and Fañanás' cells (at a postnatal age of about 4 months). Both these

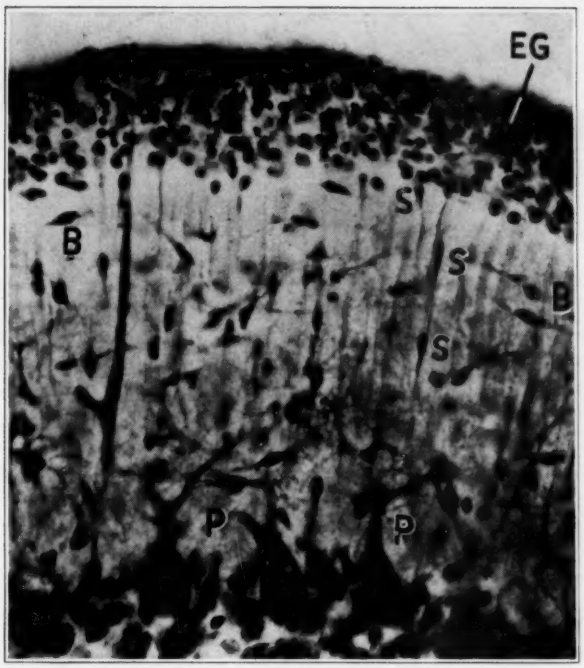


Fig. 15.—The cerebellar cortex of an infant 5 weeks old. Two cell types are now emerging from the external granular zone (*EG*). The spherical and flattened elements (*B*) with expansions parallel to the surface will form basket cells. The elongated spindle-shaped elements (*S*) perpendicular to the surface are spongioblasts.

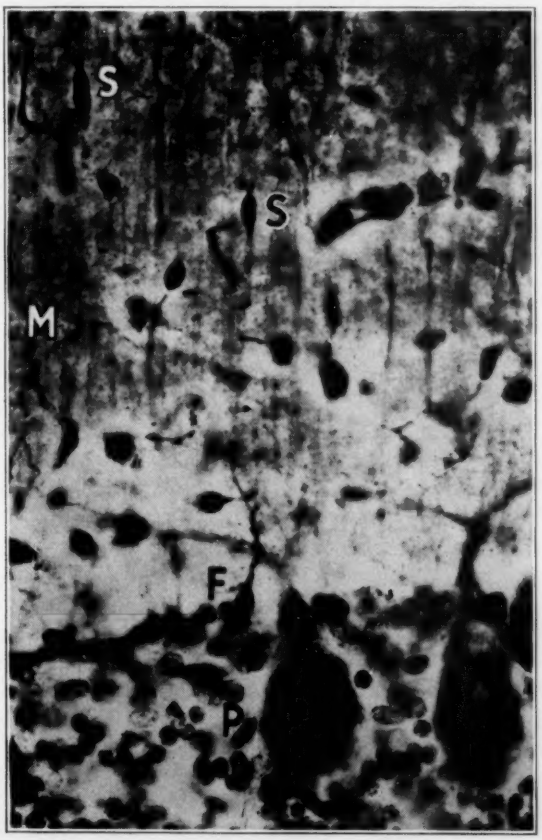


Fig. 16.—Cerebellar cortex of an infant aged 4 months. *F* indicates immature Fañanás cells derived from spongioblasts; *M*, the molecular zone; *P*, Purkinje cells, and *S*, a spongioblast.

types of astrocytes now began to accumulate in the lowest part of the molecular layer and in the Purkinje cell zone.

Both the morphologic character and the biologic behavior showed these elongated spindle-shaped elements to be spongioblasts. In some, the external expansions formed a subpial foot, and the process gradually became a Bergmann fiber (fig. 17 *G E*). In others, secondary feathery branches were formed from the main process, and the cells became Fañanás astrocytes (fig. 17 *F*). Occasionally a mitotic figure was seen in these spindle-shaped spongioblasts during migration through the molecular zone.

From these observations it is evident that the cells of the external granular zone are undifferentiated and bipotential. They are derived from neuroepithelial cells of the posterior tip of the roof of the fourth ventricle, migrate away from

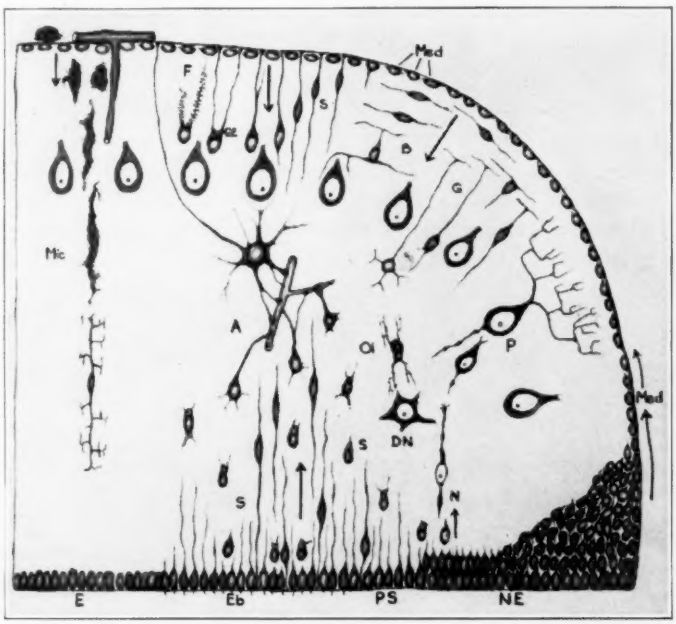


Fig. 17.—Diagram illustrating cytogenesis in the cerebellum. *A* shows astrocytic development; *B*, basket cells; *DN*, deep nuclei of the cerebellum; *E*, the ependyma; *Eb*, ependymoblasts; *F*, Fañanás cells; *GE*, a Golgi epithelial cell; *Med*, medulloblasts; *Mic*, microglial development; *N*, neuroblast forms; *Ol*, oligodendroglial development; *P*, a Purkinje cell; *PS*, primitive spongioblasts, and *S*, spongioblast forms, apolar and polar.

Medulloblasts originating from the neuroepithelium of the roof of the fourth ventricle form the external granular zone. From these medulloblasts are derived granule cells, basket cells and spongioblasts. The latter form the Golgi epithelial cells (*GE*) and Fañanás cells (*F*). The rest of the cerebellum is formed in the same way as the spinal cord and cerebrum. As in the spinal cord and brain, microglia cells are derived from mesenchymal elements and begin as ameboid cells, which invade the nerve parenchyma when intracerebral blood vessels make their appearance.

the ependymal zone and, at some distance from it, divide by mitosis and give rise to both neuroblasts (forming granule and basket cells) and spongioblasts (forming Golgi-Bergmann and Fañanás cells). They therefore satisfy the criteria of Schaper's indifferent cell and may properly be referred to as medulloblasts (fig. 17).

Except for the cortex, the substance of the cerebellum is formed in the same way as the cerebrum and the spinal cord. The deep nuclei and interstitial cells are derived by the direct migration of neuroblasts and spongioblasts originating from the cells in the ependymal zone lining the roof of the fourth ventricle (fig. 17). Purkinje cells seem to be derived from the same source.

COMMENT

The cytogenesis of the human central nervous system was studied to see if there was any evidence of the existence of Schaper's indifferent cell, the "medulloblast" of Bailey and Cushing. The silver carbonate technic of Hortega and its many modifications, supplemented by dye stains and neurofibrillar methods, were used.

Cells are fluid, moving, dynamic elements, especially during embryologic development. It is admittedly difficult to gain an insight into normal growth phenomena by the study of fixed sections. The artefacts inherent in these methods have been constantly borne in mind, and a tremendous number of cytologic gradients were observed before drawing conclusions regarding the changes and migrations of cells.

Spinal Cord and Brain.—The brain and spinal cord follow a similar pattern in cytogenesis (fig. 8). Because Schaper was unable to observe any differentiation among the cells forming the first anlage of the mantle zone, he concluded that they were all "indifferent" cells from which neurons and glia cells were later formed. Progressive improvement in histologic technic has advanced the ability to recognize differentiated cells at constantly earlier stages. Cajal [38] demonstrated by means of special stains that neuroblasts can be distinguished in the spinal cord of chick embryos much before dye stains reveal any differentiation. The earliest forms were apolar neuroblasts occurring in the ependymal region. This work was confirmed by Cowdry [39] and Tello [40] in chick embryos, by Windle and Baxter [41] in rat embryos and by Tello [29] in mouse embryos.

38. Ramón y Cajal, S.: Sur l'origine et les ramifications des fibres nerveuses de la moelle embryonnaire, Anat. Anz. **5**:111 and 609, 1890; footnote 9a.

39. Cowdry, E. V.: The Development of the Cytoplasmic Constituents of the Nerve Cells of the Chick: I. Mitochondria and Neurofibrils, Am. J. Anat. **15**:389, 1914.

40. Tello, J. F.: Les différenciations neuronales dans l'embryon du poulet, pendant les premiers jours de l'incubation, Trav. du lab. de recherches biol. de l'Univ. de Madrid **21**:1, 1923.

41. Windle, W. F., and Baxter, R. E.: The First Neurofibrillar Development in Albino Rat Embryos, J. Comp. Neurol. **63**:173, 1936.

The present study has demonstrated that in human embryos the youngest recognizable neuroblasts are also apolar cells. In the spinal cord they are constantly observed in the ependymal region at an age when well formed nerve cells are already present in the anterior horns. In the cerebrum the apolar neuroblasts are constantly recognized in the subependymal region. The fact that such differentiation can now be distinguished in the ependymal and subependymal zones minimizes one of Schaper's most important reasons for hypothecating the existence of indifferent cells or medulloblasts.

There were, however, a large number of non-neuroblastic apolar cells scattered through the brain and spinal cord of human embryos at various times. Their morphologic relations and development were best followed by the silver carbonate method. They originated from the ependymal region and also resulted from the mitotic division of spongioblasts. There was no evidence that neuroblasts are derived from them, and careful study revealed that ultimately they all develop into oligodendroglia cells and astrocytes. Lenhossék [42] and Kölliker [43] were probably the earliest to recognize such cells when they described small round apolar germinal elements which acted as supplementary sources of astrocytes. The "seal ring" cells described by Hardesty [44] in pig embryos, which formed cells that are now known to be oligodendrocytes, were probably of the same nature.

Penfield [26] first defined these apolar elements as migratory spongioblasts and demonstrated their occurrence in newborn kittens. These wandering apolar elements in the brain and spinal cord of human embryos appear at a much earlier time in development, but from their morphologic appearance and their biologic behavior they are spongioblasts. In no sense do they fit the criteria of the bipotential neurogenetic and gliogenetic medulloblast.

During the latter half of fetal life a larger type of "apolar" cell appears in the brain. This has been described by Rydberg [36] as a "naked nucleus" and has been called by many a bipotential element. The present study showed that this cell, when completely stained, has a well defined cell body and behaves as a spongioblast, giving rise exclusively to glial elements.

The occurrence of extraependymal mitoses was advanced by Schaper and others as evidence of the existence of a bipotential element in extra-

42. von Lenhossék, M.: Zur Kenntnis der Neuroglia des menschlichen Rückenmarkes, Verhandl. d. anat. Gesellsch. **5**:193, 1891.

43. Kölliker, A.: Handbuch der Gewebelehre des Menschen. ed. 6, Leipzig, Wilhelm Engelmann, 1889-1902.

44. Hardesty, I.: On the Occurrence of Sheath Cells and the Nature of Axone Sheaths in the Central Nervous System, Am. J. Anat. **4**:329, 1905.

ependymal regions. Altmann,[45] Vignal,[46] His [47] and Lenhossék [48] could not identify such mitoses. Hamilton,[30], Hatai,[31] Addison and Allen [49] made systematic studies of mitoses in the central nervous system of rat embryos and observed them in both neuroblasts and spongioblasts at various levels, but especially in the subependymal region of the hemispheres and in the external granular zone of the cerebellum. Tilney and Kubie [50] reported extraependymal mitoses in the cerebral hemispheres of cat embryos up to 95 mm., and Jones [51] observed them in a 4 day mouse. In human infants Donaldson [52] stated that mitotic division is still in progress in the brain for the first eighteen months of postnatal life.

In the present study, many extraependymal mitoses were observed. With successful silver carbonate stains the dividing nucleus and the surrounding protoplasm could be impregnated simultaneously. Although most cells retract their expansions at the moment of actual division, many polar cells were observed in various stages of mitoses, and in this way it was possible to identify these cells and their products (fig. 11). In the brain and spinal cord it was evident that spongioblasts divide extensively by mitosis. Many mitotic figures occurred even in multipolar spongioblasts. In addition, in the subependymal region of the brain neuroblasts were also seen dividing by mitosis.

It is significant that in the spinal cord the extraependymal mitoses were predominantly in the marginal zone and occurred during the period of rapid formation of oligodendroblasts. In the cerebral hemispheres they were most frequent in the subependymal zone, and some occurred in the lower intermediary region. None were seen in the outer half of the intermediary zone or in the cortical plate. In the latter areas it seemed clear that the cells all arrived by migration from periependymal regions, and no new elements were formed in situ.

There is therefore no evidence of a "medulloblast" in the brain and spinal cord.

---

45. Altmann, cited by Schaper.[2b]

46. Vignal, W.: Sur le développement des éléments des couches corticales du cerveau et du cervelet chez l'homme et les mammifères, Arch. de physiol. norm. et path. **2**:228 and 311, 1888.

47. His.[11] His.[12]

48. von Lenhossék, M.: Der feinere Bau des Nervensystems, ed. 2, Berlin, Gustav Fischer, 1895; footnote 42.

49. Allen, E.: The Cessation of Mitosis in the Central Nervous System of the Albino Rat, J. Comp. Neurol. **22**:547, 1912.

50. Tilney, F., and Kubie, L.: Behavior in Relation to the Development of the Brain, Bull. Neurol. Inst. New York **1**:229, 1931.

51. Jones, O. W., Jr.: Cytogenesis of Oligodendroglia and Astrocytes, Arch. Neurol. & Psychiat. **28**:1030 (Nov.) 1932.

52. Donaldson, H.: Growth Changes in Mammalian Nervous System, in Harvey Lectures, 1916, Philadelphia, J. B. Lippincott Company, 1917, vol. 12, p. 133.

Cerebellum.—The cytogenesis of the cerebellum is summarized in figure 17. It has been possible to confirm Schaper's contention that the cells of the external granule zone are bipotential, and the term medulloblast may justifiably be applied to them.

That Cajal was never able to demonstrate the formation of spongioblasts and astrocytes from the external granule zone is less surprising than seems at first sight. These cells are refractory to gold stains until the mature Golgi astrocytes are present. The cells of Fañanás were described only in 1916, several years after Cajal did most of his work on cerebellar histogenesis. The intermediary spongioblasts described here and derived from the superficial granular zone can be stained with any degree of completeness only by silver carbonate methods. These spongioblasts are distinguished from the granule and basket cells by the fact that they do not make their appearance till almost at birth; they are elongated cells the long axis of which is perpendicular to the surface from the start, and they have spindle-shaped nuclei and polar expansions. They do not migrate through the Purkinje cell layer. No Golgi astrocytes or Fañanás cells are seen until these spongioblasts come to rest at or just above the Purkinje zone and are gradully transformed into the special astrocytic forms.

Medulloblastoma.—That the medulloblast is a cell peculiar to the developing cerebellar cortex is substantiated by the fact that the medulloblastoma is almost exclusively a tumor of the cerebellum (Bailey and Cushing;[1a] Penfield,[53] and Elvidge, Cone and Penfield[54]). Originally, a few examples of this tumor in the cerebrum were described by Bailey and Cushing,[1b] but these have since been reclassified (Cushing[55]) as obligodendrogliomas, neuroepitheliomas and neuroblastomas. Some of them, however, do not fit any of these groupings, and a possible reason will be suggested later. Bailey[56] now believes that medulloblastomas are all primarily cerebellar.

Although certain authors prefer another name for this tumor, most agree that it arises from a polyvalent cell and that both neuroblasts and spongioblasts are present in it. Thus, Marburg[57] called it a sphero-

53. Penfield, W.: Principles of the Pathology of Neurosurgery, in Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1927.

54. Elvidge, A. R.; Cone, W. V., and Penfield, W. G.: The Gliomas of the Central Nervous System: A Study of Two Hundred and Ten Verified Cases, A. Research Nerv. & Ment. Dis., Proc. **16**:107, 1935.

55. Cushing, H.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

56. Bailey, P.: Personal communication to the author.

57. Marburg, O.: Zur Kenntnis des sogenannten Medulloblastoms, Deutsche Ztschr. f. Nervenh. **117-119**:289, 1931.

blastoma, and Roussy, Oberling and Raileanu [58] preferred the term neurospongioma, as did Ostertag.[59] Neither of these terms has any particular advantage over medulloblastoma.

Roussy, Oberling and Raileanu and Ostertag expressed the belief that usually differentiation is mainly on the neuroblast side. Stevenson and Echlin [60] recently reported on a series of cerebellar tumors, some of which were previously regarded as medulloblastomas, in which they concluded that there was evidence only of neuroblast formation. They therefore proposed the term neuroblastoma or granuloblastoma (since they arose from the external granular zone) for these tumors.

It is a fairly common experience at the Montreal Neurological Institute to find that some medulloblastomas undergo a more selective trend toward neuroblast formation than others. This should not be surprising, however, as during normal development the neuroblasts forming granule and basket cells are numerically the main derivatives of the medulloblasts of the external granular zone. The migration of spongioblasts occurs only during a relatively short period and is numerically much less. It is more surprising that in medulloblastomas one should find nerve cells showing intracellular neurofibrils and Nissl substance. In normal granule cells the intracellular neurofibrils are extremely difficult to demonstrate, and Nissl substance does not occur. Similarly, the astrocytes occasionally seen in medulloblastomas are not of the same type as the peculiar astrocytes normally derived from the external granular zone. This is probably because in tumors the special conditions of normal growth (such as the existence of Purkinje cells with "candelabra" expansions) are not present to initiate or influence their formation. This is further evidence that although tumor cells may imitate or resemble embryonic cell types, the imitation is often only grotesque and distorted.

Before leaving this subject, it should be mentioned that in areas like the *Ganglienhügel,* where there is great widening of the ependymal zone, the peripheral cells may lose their connection with the ventricular wall and superficially resemble medulloblasts. But there is no evidence that these migrate to more peripheral zones before differentiating. However, tumors derived from these cells may conceivably resemble medulloblastomas rather than neuroepitheliomas.

The Primitive Spongioblast and Germinal Cell of His.—These two terms, coined by His, still have wide currency. Their definition, in view of subsequent work, requires reevaluation. It is now abundantly clear

58. Roussy, G.; Oberling, C., and Raileanu, C.: Les neurospongiomes, Presse méd. **39**:977, 1931.

59. Ostertag, B.: Einteilung und Charakteristik der Hirngewächse, Jena, Gustav Fischer, 1936.

60. Stevenson, L., and Echlin, F.: Nature and Origin of Some Tumors of the Cerebellum: Medulloblastoma, Arch. Neurol. & Psychiat. **31**:93 (Jan.) 1934.

that the germinal cell represents the form in which the neuroepithelial cell divides, rather than the specific precursor of neuroblasts, as was maintained by His. Recently, Sauer [61] demonstrated that when the ependymal zone is multilayered the cell bodies of the columnar epithelial elements migrate to the internal limiting membrane when undergoing mitosis.

Because the first-formed primitive columnar cells are capable of producing both neuroblasts and spongioblasts, the term primitive spongioblasts, which His applied to them, is misleading. This name should be reserved for the cells remaining at the ependymal zone which are capable only of producing spongioblasts and ependymal elements, after formation of neuroblasts has ceased. Up to that time, the term neuroepithelium is more appropriate and descriptive of the potentialities of these cells.

During the embryologic development of the brain and spinal cord there occurs another large group of cells, which ordinary dye stains do not demonstrate completely and which might create the impression of apolar indifferent cells. Silver carbonate stains show that these are microglia cells; they occur from the time of the earliest appearance of intracerebral blood vessels. They originate from mesenchymal cells and will be the subject of a separate study (Kershman [62]).

Finally, it is obvious from the foregoing discussion that in this study the cells were observed to be units from the start and remained so throughout development into adult life. Special stains did not confirm the existence of the neurospongium or syncytium described by some authors, notably His, Hardesty, Streeter,[63] Bok [64] and, more recently, Rydberg.[36]

SUMMARY AND CONCLUSIONS

1. The term medulloblast was given by Bailey and Cushing to the "indifferent cell" of Schaper. It designates an apolar, bipotential, undifferentiated element which is supposed to leave the ependymal zone during development and migrate through the central nervous system, later differentiating into neuroblasts and spongioblasts. Some of these cells were said by Schaper to persist through adult life.

---

61. Sauer, F. C.: Mitosis in the Neural Tube, J. Comp. Neurol. **62**:377, 1935.

62. Kershman, J.: Genesis of Microglia in Human Embryos, Arch. Neurol. & Psychiat., to be published.

63. Streeter, G.: Development of the Central Nervous System, in Keibel, F. K. J., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 1.

64. Bok, S. T.: Das Rückenmark, in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1928, vol. 4, p. 478.

2. Medulloblasts could not be identified in the spinal cord or cerebral hemispheres of the growing human brain.

3. In the cerebellum, the external granular zone is a transitory zone composed of cells which are derived from the neuroepithelium of the roof of the fourth ventricle. These cells migrate in an undifferentiated state and later divide by mitosis and produce both neuroblasts and spongiobasts. These cells of the external granular zone may justifiably be called medulloblasts.

4. The external granular zone of the cerebellum is the only location in which medulloblasts could be identified.

5. This is in harmony with the fact that medulloblastomas *occur exclusively* in the cerebellum.

6. The cells described by His as primitive spongioblasts and germinal cells should, in the light of present knowledge, be called neuroepithelial cells. The germinal cell is the latter in mitotic division. The term spongioblast should be retained for exclusively neuroglial progenitors.

7. The apolar migratory spongioblast plays an important role in glial development, and in the cerebral hemispheres is numerically the most important glial precursor. It is probably this cell that Schaper concluded was indifferent and bipotential in the brain and spinal cord.

8. Apolar spongioblasts are derived from neuroepithelial cells, from primitive spongioblasts and ependymoblasts and by proliferation from previously formed spongioblasts. They are capable of mitotic division and give rise to all forms of spongioblasts, to oligodendroglia cells and to astrocytes.

9. Spongioblasts are plastic, mobile cells, which during development may vary in shape and be apolar, unipolar, bipolar or multipolar (the last being distinguished from astrocytes by the absence of vascular feet). All these types are essentially variants of the same element.

10. Both spongioblasts and young neuroblasts can divide by mitosis during embryonic development.

MYOCLONIC EPILEPSY

ROY R. GRINKER, M.D.

HERMAN SEROTA, M.D.
AND
SAM I. STEIN, M.D., PH.D.
CHICAGO

From a chaotic group of hyperkinetic manifestations Friedreich separated an entity which was characterized by rapid, lightning-like twitchings of the muscles, or myoclonia. This syndrome, now known as Friedreich's paramyoclonus multiplex, he ascribed to abnormal irritability of the cells of the anterior horn. In 1891 Unverricht [1] demarcated still another nosologic entity of myoclonic phenomena associated with epilepsy. He described several cases from the previous literature and added observations on a family composed of 5 sisters. These patients were afflicted between the ages of 6 and 13 years, first with generalized convulsions, followed in a few years by the onset of myoclonia consisting of irregular, arrhythmic lightning-like jerks of muscle groups without movements of the extremities. These affected both upper extremities first and involved the face last. Sleep abolished the movements; external disturbances, psychic upsets and volitional muscular effort increased them. Unverricht, too, expressed the belief that the myoclonia is the result of increased irritability of the anterior horn cells.

Since 1891 many cases have been described clinically by Westphal,[2] Pilotti,[3] Marchand [4] and others, so that there is no doubt as to the validity of the entity known as Unverricht's familial myoclonic epilepsy. There are, however, other types of myoclonic epilepsy and they may be classified as follows: (1) intermittent myoclonia of Lundborg; (2) partially continuous myoclonia of Kojewnikow, and (3) progressive familial myoclonia of Unverricht.

Read before the Central Neuropsychiatric Society, Oct. 8, 1937.

From the Department of Neuropsychiatry of the Michael Reese Hospital.

1. Unverricht, H.: Die Myoclonie, Berlin, Franz Deuticke, 1891; Ueber familiäre Myoclonie, Deutsche Ztschr. f. Nervenh. **7**:32, 1895.

2. Westphal, A.: Ueber eigenartige Einschlüsse in den Ganglienzellen (Corpora amylacea) bei einem Falle von Myoklonusepilepsie, Arch. f. Psychiat. **66**: 769, 1919.

3. Pilotti, G.: Sulla presenza di corpi palini nel protoplasma delle cellule nervose del midollo spinale un caso di policlonia, Riv. sper. di freniat. **45**:421, 1922.

4. Marchand, L.: Les myoclonies épileptiques, Encéphale **29**:217, 1934.

The first type, that of Lundborg, asserts itself as a myoclonic aura of a major epileptic seizure or as a motor epileptic equivalent. It is not progressive. The second type consists of constant isolated movements of the muscles affected, which seem to be sequelae of a local cortical inflammatory process. Extirpation of the area of the cortex involved abolishes the local hyperkinesis.[5]

The type described by Unverricht is an inherited disease of a mendelian recessive order, according to Lundborg.[6] It appears most frequently in girls. It begins before puberty with generalized epileptic attacks and only rare myoclonic jerkings in the first stage. After from one to five years the second stage of myoclonia begins, in which the twitchings appear, increasing in intensity and frequency and gradually involving the entire body. Gradual diminution of intelligence occurs. In the terminal stage involvement of the bulbar musculature may cause death after the entire syndrome has lasted from ten to twenty years. Intelligence becomes profoundly altered, ending in the usual picture of organic dementia. Other signs of degeneration appear in the form of symptoms of extrapyramidal and cerebellar disturbance, such as tremor, ataxia, asynergia, etc., as recently described by Hodskins and Yakolev.[7] These authors added that the disease should be considered an amyostatic syndrome because there are signs of extrapyramidal involvement and the myoclonus readily appears on change of posture.

The pathologic picture of myoclonic epilepsy has been described by Lafora and Glueck,[8] Westphal and Sioli,[9] Marchand[10] and others. Hodskins and Yakolev[7] tabulated 18 cases occurring between 1911 and 1928 in which necropsy was performed. In general, many types of degenerative changes have been seen in the brain, in all the elements; even softenings have been described. However, characteristic in all the pathologic studies was the observation of spherical inclusion bodies

5. Grinker, R. R.: Neurology, ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1937, p. 840.

6. Lundborg, H.: Der Erbgang der progressiven Myoklonus-Epilepsie (Myoklonie-Epilepsie s. Unverrichts familiäre Myoklonie), Ztschr. f. d. ges. Neurol. u. Psychiat. **9**:353, 1912.

7. Hodskins, M. B., and Yakolev, P. I.: Anatomico-Clinical Observations on Myoclonus in Epileptics and on Related Symptom Complexes, Am. J. Psychiat. **9**: 827, 1930.

8. Lafora, G. R., and Glueck, B.: Beitrag zur Histopathologie der myoklonischen Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **6**:1, 1911.

9. Westphal, A., and Sioli, F.: Weitere Mitteilung über den durch eigenartige Einschlüsse in den Ganglionzellen (Corpora amylacea) ausgezeichneten Fall von Myoklonusepilepsie, Arch. f. Psychiat. **62**:1, 1921.

10. Marchand, L.: Dégénérescence amyloïde de la cellule nerveuse, Ann. d'anat. path. **12**:1, 1935.

within the ganglion cells. Inclusion bodies have been seen in cells in almost every part of the brain, but in most reports there was more specific localization in the dentate nucleus of the cerebellum, the optic thalamus, the nucleus ruber, the substantia nigra and other basal nuclei. However, in some cases the cerebral cortical cells were also involved. The spinal cord was rarely implicated.

These bodies were for some time believed to be characteristic of and specific to myoclonic epilepsy. Although they invariably appear in this disease, they have been described within the brain tissue in many other conditions, but in myoclonic epilepsy, unlike other diseases, inclusion bodies appear within the ganglion cells and are especially numerous in the aforementioned gray masses.

The inclusion bodies are corpora amylacea, or amyloid bodies. They are spherical, with layers which seem to increase with the age of the bodies. Hematoxylin and eosin stains demonstrate them well. They have an affinity for iodine and take Best's stain for glycogen, although, unlike glycogen, they are insoluble in water. Also, like fatty acids, they are stained intense red with neutral red. Spielmeyer [11] stated that these histochemical reactions suggest that the amyloid bodies are mixtures of sphingomyelin and phrenosin and a glycogen or carbohydrate body. They are observed in elderly persons and exist in the glia as phagocytosed foreign bodies, not arising from the glia. Their presence indicates a chronic regressive process in the central nervous system, and they are probably catabolic products associated with changes allied to senility.

We wish to report on a family in which there were 2 living persons with myoclonic epilepsy and several epileptic persons in the same and previous generations. This family was studied clinically and with the encephalographic technic, by means of which the position of myoclonic epilepsy in the group of convulsive states is hypothecated.

REPORT OF CASES

Case 1.—E. G., a white woman aged 28, married, was admitted to the Michael Reese Hospital on Jan. 25, 1937, complaining of pulling pains in the right side of the abdomen, nervous twitchings of the muscles of the face, head and extremities and spells of unconsciousness. The first attack began at the age of 15, a few weeks before the first menstrual period. In this attack no aura or tonic or clonic contractions appeared. Within a few months spontaneous twitchings in the muscles of the extremities were noted. Objects dropped from the hands; the gait became unsteady, and the patient often fell. A second attack of unconsciousness occurred one year later, after which medication was taken which prevented further seizures. At the age of 21 the patient was delivered of a child normally. Four days later a generalized convulsion appeared and was

11. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922.

followed by unconsciousness lasting fifteen minutes. Phenobarbital was prescribed; when taken regularly this decreased the major seizures and muscular twitchings. However, in the last six years there had been about twelve attacks, occurring at intervals of six months. None had appeared during the two years prior to hospitalization. Unsteadiness and muscular twitchings increased in intensity, especially when no medication was taken. Headache and loss of memory became progressively more marked. Mental symptoms dated from the age of 16, when lapses of memory and inability to concentrate and to make ordinary calculations were noted. The patient also became sexually promiscuous.

In 1923 the patient had undergone appendectomy, and in 1929, thyroidectomy and tonsillectomy.

The mother was living and well; she knew of no epilepsy in her family. On the father's side, a decided convulsive tendency was noted: The paternal grandmother had major epilepsy and killed one of her children. The father had local muscular, especially facial, twitchings, but no major seizures; he committed suicide during a period of depression. There were 2 normal brothers, aged 32 and 33. A sister aged 18 had a miscarriage during the seventh month of pregnancy because of eclampsia. A sister, born in 1907, died at the age of 1 year of convulsions complicating pertussis. A son, aged 6 years, was normal.

Examination.—The patient was well developed, but subdued. Speech was slurring and stuttering. Gait was shuffling with a broad base, and the arms were held rigidly at the sides. The first and second cranial nerves were normal. The eyes showed vertical nystagmus. The right pupil was larger than the left, but the pupillary reactions were normal. The right masseter muscle was slightly weak, and the facial muscles were paretic on the right. Both the achilles and the patellar jerk were absent; otherwise the reflexes were normal, and no pathologic reflexes were elicited. Sensation for touch and pain was slightly diminished on the right side. Slight incoordination was noted in movements of all extremities.

Myoclonia: On the patient's admission to the hospital, under the influence of phenobarbital, 3 grains (0.194 Gm.) daily, no myoclonic jerkings were noted. The medication was stopped, and in forty-eight hours the patient complained of supraorbital and frontal headaches. Mild myoclonic jerkings appeared about the mouth and on the right side of the face. By the third day the twitchings were more continuous and violent and caused gross movements of the extremities. The patient could not walk without stumbling, falling and hurting herself. On the fourth day a major convulsion was ushered in by a loud scream, and unconsciousness lasted for ten minutes. The convulsion consisted of generalized tonic and clonic contractions, which were more severe on the right side. Thereafter the myoclonia disappeared for four hours. Gradually the myoclonic jerks increased in intensity, terminating in two days in another seizure—a rhythm which repeated itself until phenobarbital was again prescribed.

When the patient was readmitted to the hospital on Aug. 20, 1937, for electroencephalographic studies, the rhythm described was observed several times when phenobarbital was withheld. Gradually the myoclonia increased in frequency and intensity, culminating in a major epileptic attack followed by a quiescent period, after which the myoclonia gradually reappeared. One exception was noted in which an epileptic attack occurred when the patient was free from myoclonus.

Psychometric examination by Dr. Sam Beck showed a score of 61 on the Army alpha scale, or 14 years and 2 months on the Binet scale. Scoring in the subtests was uneven, showing probable uneven intellectual functioning.

Laboratory Findings.—The Wassermann and Kahn reactions of the blood were negative. Examination of the blood revealed: red cells, 3,800,000; hemoglobin,

60 per cent; white cells, 8,000; fasting level of sugar, 83 mg. per hundred cubic centimeters; nonprotein nitrogen, 30 mg.; chlorides, 490 mg.; cholesterol, 264 mg.; calcium, 10.5 mg., and phosphorus, 3.4 mg. The urine was normal. The cerebrospinal fluid was clear and was under a pressure of 250 mm. of water with the patient in the sitting posture; the Wassermann reaction of the fluid was anticomplementary; the colloidal gold curve was 0001222100; the value for sugar was 67 mg., for chlorides 721 mg. and for total protein 35 mg.

Roentgenographic Examination.—The pineal body was calcified, but not shifted. There were faint frontal hyperostoses, but otherwise the skull was normal. Pneumoencephalographic examinations showed no abnormality except slight uniform dilatation of the cerebral ventricles.

Biopsy of the Cerebral Cortex.—With the patient under local anesthesia, a burr hole was made in the parieto-occipital region, the dura opened and a section of cortex removed. The material was cut and stained by the usual methods.

Microscopic examination showed a few traumatic capillary hemorrhages. The blood vessels, however, were normal. The leptomeninx was moderately thickened with fibrous connective tissue. The architecture of the cortex was disturbed by the fact that in all layers many cells had fallen out. The neuroglia showed no marked changes. There were clusters of pericellular satellitic oligodendroglia cells, but no increase or progressive change in the astrocytes was noted. The microglia cells were not unusual. The ganglion cells showed marked degenerative changes. For the most part these consisted in shrinking of the cell bodies into angular and distorted shapes. The cytoplasm of the cells revealed no distinct Nissl bodies, but stained homogeneously dark blue. The nuclei were often absent or were represented only by peripherally placed pyknotic spheres. Other cells were swollen and rounded and had faintly stained, washed-out cytoplasm with fine chromatin granules. No inclusion bodies were observed in the ganglion cells.

CASE 2.—A. K., the father's sister, was 52. Convulsive seizures began at the age of 4 years. She was thin and rather dilapidated in appearance and seemed older than her chronologic age. She was markedly deteriorated mentally. Examination revealed marked facial hirsutism. There was considerable peripheral arteriosclerosis. The muscular strength was generally reduced. As the patient lay on the couch there were abrupt flinging movements of the upper extremities, involving the fingers, hand and entire arm. The legs were likewise involved. There were rapid myoclonic movements of the facial muscles, which could be produced by local stimulation. There were blinking movements of the eyes and twitchings of the lips. Twitchings of the muscles of the neck resulted in jerking of the head. On attempting to initiate any type of voluntary movement, flinging of the extremity became marked. The deep and superficial reflexes were all absent. The cranial nerves were normal.

DESCRIPTION OF THE ELECTROENCEPHALOGRAMS (FIGS. 1 AND 2)[12]

Mother.—From the occipital region rapid alpha waves, at a frequency of 15 per second, were obtained. These were of low voltage, from 25 to 50 microvolts. There were many fast beta waves and slow waves appearing at a frequency of from 1 to 2 per second, or even 1 per two seconds. The frontal lead revealed rare alpha waves appearing in bursts with a frequency of 15 per second and an amplitude of from only 25 to 35 microvolts. There were few fast waves and a moderate number of slow waves of from 1 to 3 per second (fig. 1 *A, K.*).

12. All electroencephalograms are to be read from right to left.

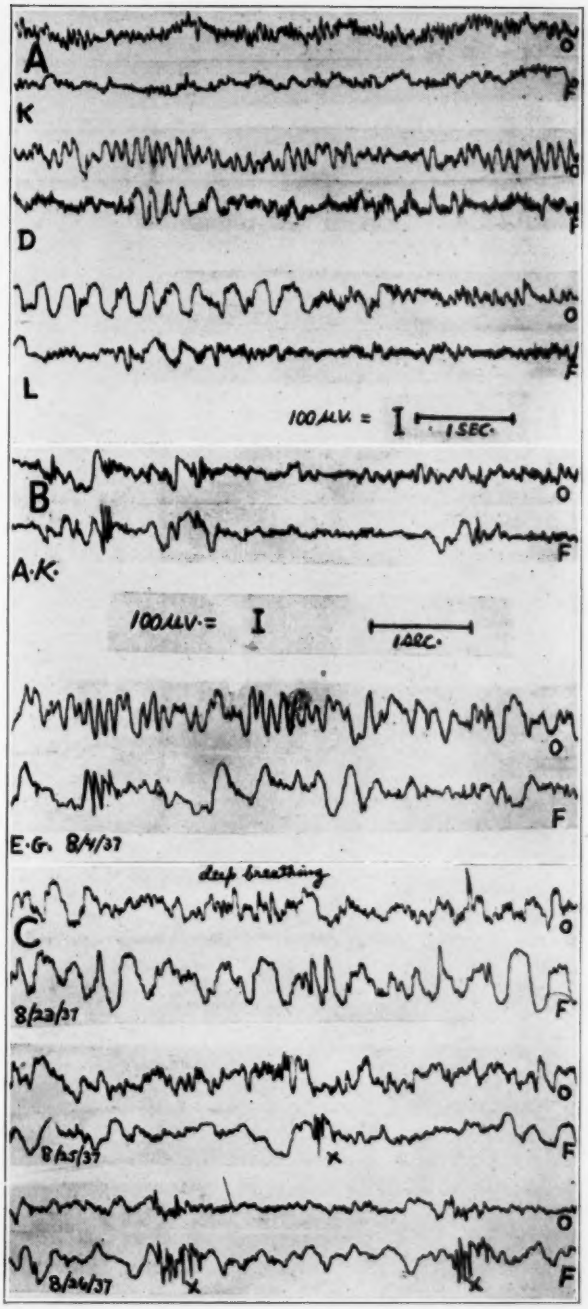


Fig. 1.—In this figure and in figure 2, the tracings are to be read from right to left. Time and microvoltage are indicated below the tracings. *O* denotes the occipital region and *F*, the frontal region. See text for description.

A: tracings for (*K*) the patient's mother, (*D*) the patient's son and (*L*) the patient's sister, who had eclampsia.

B: tracings for(*A. K.*) the patient's myoclonic aunt and (*E. G.*) the patient when under the influence of phenobarbital. (*8/25/37*).

C: tracings for the patient (*8/23/37*) when in the hospital under the influence of phenobarbital, showing the effect of deep breathing, and two days (*8/25/37*) and three days (*8/26/37*) after the cessation of phenobarbital. *X* designates the clusters of spikes.

Son (aged 6).—The occipital lead showed good alpha waves of 100 microvolts, appearing at a frequency of 9 per second. There were few fast waves, and slow waves, though present, were rare. The frontal lead showed occasional alpha waves; there were many fast waves and slow waves appeared at a frequency of 3 per second in groups lasting from one to two seconds (fig. 1 *A, D.*).

Sister (eclamptic).—The electroencephalographic configuration was of the mixed type, showing 10 per second alpha waves from the occipital lobes. In the frontal lobe there were plainly seen fast waves and rare alpha waves. Strikingly shown in this tracing was the fact that deep breathing produced in a short latent period of two seconds loss of alpha waves and large 4 per second waves (fig. 1 *A, L.*), especially in the occipital lead.

Aunt (case 2, myoclonic).—There was marked irregular fluctuation in alpha waves of from 8 to 10 per second and from 25 to 40 microvolts in amplitude. The frontal region showed large irregular waves and clusters of spikes, 200 microvolts in amplitude, as well as characteristic cusp and dart formations (fig. 1 *B, A. K.*).

Patient (case 1, myoclonic).—The last attack occurred before the second admission, on July 26, 1937.

August 4 (patient still under treatment with phenobarbital): Occipital alpha waves of 9 per second and from 100 to 230 microvolts were irregularly mixed with large waves of from 4 to 5 per second and of from 250 to 300 microvolts. The frontal lobe showed rare alpha waves. There were sporadic, often grouped, large complex waves lasting half a second and with an amplitude of from 250 to 300 microvolts (fig. 1 *B, E. G.*).

August 23 (patient in hospital under treatment with phenobarbital): There were fewer occipital alpha waves and more fast waves. The large frontal waves appeared at a frequency of 3 per second (fig. 1 *C*).

August 25 (two days after medication was stopped): The large irregular waves were more frequent. Occasionally spiked waves appeared (fig. 1 *C*).

August 26 (three days after medication was stopped): The patient was unsteady, with difficulty in speech, which was hesitant and stuttering. There was markedly increasing myoclonia. Spikes were more frequent, the bursts lasting four-tenths seconds, with an amplitude of 200 microvolts. They occurred at irregular intervals, many three seconds apart. Spikes were most marked in the frontal region, but there was a suggestion of their synchronous appearance in the occipital lobe. There were also 6 per second waves superimposed on large 2 per second waves. Alpha waves appeared at a frequency of 9 per second and with an amplitude of from 25 to 30 microvolts (fig. 1 *C*). At 5:30 p. m., five hours later, there was greater synchrony between the spikes in the frontal and those in the occipital lead. Those from the occiput were from 100 to 150 microvolts in amplitude, and those from the frontal lobe from 200 to 250 microvolts. The bursts of spikes were more regular, with three second intervals. There were also large irregular waves (fig. 2 *A*).

August 27 (four days after medication was stopped): At 12:30 p. m. the bursts of spikes were one second in duration and were synchronous in the two leads. Those from the frontal lead were from 200 to 250 microvolts in amplitude, and those from the occipital lead, from 100 to 160 microvolts (fig. 2 *A*). An epileptic attack occurred at 3:20 p. m. Thirty minutes later there were only rare bursts of spikes, lasting twenty-five hundredths of a second, but large waves, of from 100 to 150 microvolts, dominated (fig. 2 *A, P. S. F.*).

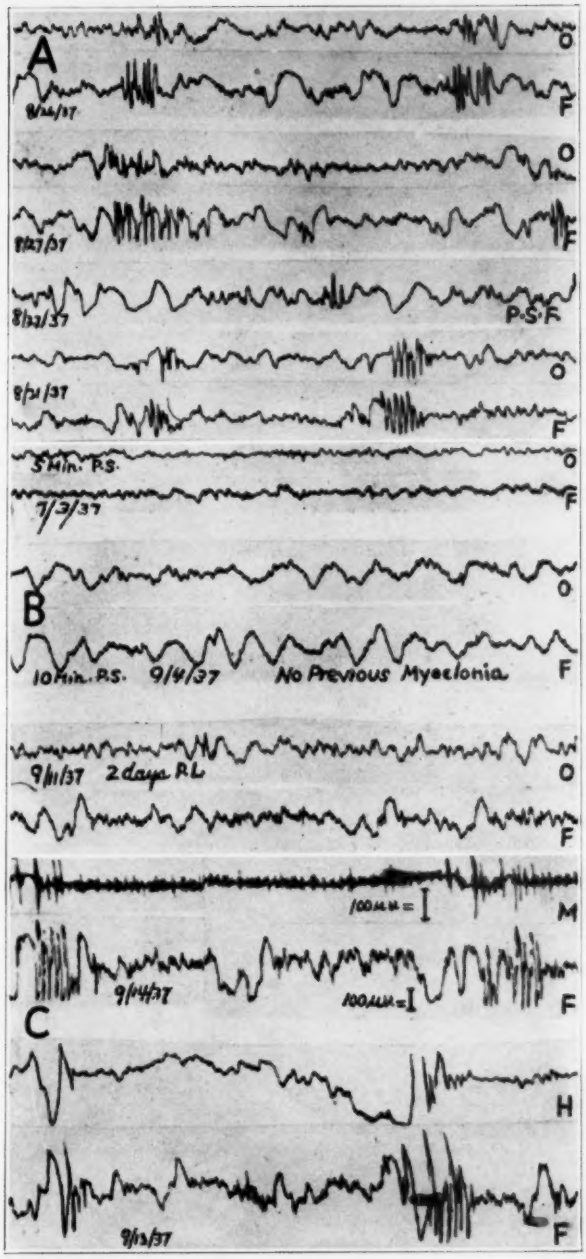


Fig. 2.—*A:* tracings taken five hours later than the last tracing in figure 1 *C* (*8/26/37*), showing occipital spikes more plainly; three hours before a major seizure (*8/27/37*), showing large bursts of spikes synchronous in the two leads; thirty minutes after an attack (*8/27/37 P. S. F.*), showing rare spikes and large slow waves, and four days after a seizure (*8/31/37*), showing recurrence of clusters of large spikes. See text for description.

B: 9/3/37, 5 min. P. S. shows a flat curve of exhaustion five minutes after a major seizure; *9/4/37, 10 min. P. S.*, the large slow waves ten minutes after a major seizure not preceded by myoclonia, and *9/11/37, 2 days P. L.*, the effect on the spikes of administration of phenobarbital for two days.

C: 9/14/37, taken during myoclonia. *M* is a lead from a muscle, and *F,* a lead from the frontal cortex. In *9/13/37 H* is a lead from the hypothalamic region, and *F,* a lead from the frontal cortex.

September 3: Five minutes after an attack there was a completely flat curve of exhaustion. The maximum amplitude was 100 microvolts; the slowest waves were from 4 to 5 per second, and there were only occasional slow waves in the occipital lobe (fig. *2 B, 5 min. P. S.*).

September 4 (ten minutes after an exceptional attack not preceded by increasing myoclonia): There were large regular waves with a frequency of 3 per second and an amplitude of 200 microvolts. This tracing resembled closely that seen in approaching sleep (fig. *2 B, 10 min. P. S.*).

September 11 (after resumption of phenobarbital, 8 grains [0.518 Gm.] per day): There were occasional alpha waves of from 9 to 10 per second, appearing in bursts with an amplitude of from 25 to 50 microvolts. In the frontal lobes there were irregular large waves of from 3 to 6 per second and slow waves of from 125 to 200 microvolts, together with plainly seen fast waves (fig. *2 B, 2 days P. L.*).

Simultaneous leads from the biceps muscle and the frontal cortex showed that the maximal burst of cortical spikes appeared simultaneously with, or slightly before, the maximal muscle twitchings (fig. *2 C, 9/14/37*).

Simultaneous hypothalamic and cortical leads showed that spikes appeared in the former after a latent period of three-tenths second (fig. *2 C, 9/13/37*).

COMMENT

The exquisitely inherited convulsive tendency is adequately illustrated by the family studied. There were, besides the patient: an epileptic, homicidal paternal grandmother; a depressed, suicidal father; a myoclonic, deteriorated aunt and 2 siblings suffering from convulsions complicating other diseases. In other respects, also, the histories of the 2 myoclonic patients were typical. The disease began with convulsions, followed by myoclonia, intellectual deterioration and cerebellar symptoms. The pathologic changes seen in the specimen taken for biopsy were those of a chronic degenerative process in the parenchyma, with no amyloid bodies. However, these bodies are notoriously observed most frequently in the basal regions at necrospy, so that their absence from the cortex is not exceptional.

Electroencephalographic studies of the family showed that the mother and the son of the patient were normal. The aunt had typical myoclonic epilepsy, with more signs of organic cerebral degeneration than the patient. The sister, whose convulsive capacity was represented clinically only by eclampsia complicating pregnancy, showed a normal electroencephalogram. However, deep breathing brought on, after a short latent period, many large slow waves similar to those seen in the 2 myoclonic members of the family.

In considering the electroencephalographic findings in myoclonic epilepsy, one is helped by the descriptions of other types of epilepsy already published. Petit mal attacks have been studied in detail by

Gibbs, Davis and Lennox,[13] who described "large approximately sinusoidal waves followed by a rapid negative deflection" appearing a few seconds before the clinical onset of the attack. This wave complex appears at a rate of about 3 a second, and the amplitude is from ten to twenty times that of the normal pattern. It persists as long as the seizure.

The findings of Berger[14] and Kornmüller[15] have been confirmed for grand mal seizures. An attack is ushered in by a series of rapid small waves, from 10 to 30 per second, which gradually increase in amplitude. With them slow waves, from 2 to 3 per second, of similar amplitude appear, at times suggesting a petit mal pattern. During the clonic phase the very large waves and their more rapid components are at a maximum, the rapid waves being most dominant during the last clonic jerks. During the postseizure stupor the rapid activity disappears.

If one characterizes grand mal by two phenomena, viz., loss of consciousness and aberrant motor discharges, one may, as a corollary, put down as milder variants of this main type the commonly occurring entity petit mal and its rarer antithesis myoclonic epilepsy.

It can be noted in figure 1 *C* to 2 *B* that after a remission, either spontaneous or induced by the use of phenobarbital, small bursts of rapid spikes, from 10 to 15 per second, make their appearance on the patient's typical electroencephalogram. Early in the course of a cycle these may be rare, only 2 or 3 of them appearing in a cluster. As time goes on, the bursts increase in amplitude; the duration of a cluster becomes longer, and the interval between bursts becomes shorter. These changes are accompanied by definite clinical myoclonic twitchings. The myoclonia is first seen as twitchings about the mouth and face, later as sudden flinging movements of the arms and then as bizarre motor discharges affecting the whole skeletal muscular system. The spikes in the electroencephalogram are synchronous with the myoclonus (fig. 2 *C*). Also, the initial focus which arises in the frontal lobes spreads so

13. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133 (Dec.) 1935. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: The Electro-Encephalogram in Diagnosis and Localization of Epileptic Seizures, ibid. **36**:1225 (Dec.) 1936. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: Effect on the Electro-Encephalogram of Drugs and Conditions Which Influence Seizures, ibid. **36**:1236 (Dec.) 1936.

14. Berger, H.: Ueber das Elektrenkephalogramm des Menschen, Arch. f. Psychiat. **87**:527, 1929; **100**:301, 1933.

15. Kornmüller, A. E.: Der Mechanismus des epileptischen Anfalles auf Grundbiolektrischer Untersuchungen am Zentralnervensystem, Fortschr. d. Neurol., Psychiat. **7**:391 and 414, 1935.

massively as to invade the occipital lobe, which then also shows the myoclonic spikes. After this crescendo of rapid activity, a major epileptic seizure results, and this in turn gives way to exhaustion and flaccidity, represented on the electroencephalogram by a flat curve, from which rapid activity is absent until the building up of a new cycle.

The grouping of petit mal and myoclonic epilepsy as opposite variants of the more spectacular grand mal attack seems obvious in the electroencephalogram. Petit mal waves are slow, appear as manifestations of a low level of consciousness and are not usually attended by motor discharges. Myoclonic waves are about five times as fast, are not associated with loss of consciousness and result in muscle twitches. Petit mal waves are brought on by hyperventilation. In myoclonic epilepsy forcible overbreathing to the point of giddiness (fig. 1 *C*) produces only slow waves, without spiked components. Focusing of attention, as in counting or talking, abolishes petit mal waves, whereas the same factors, including volition and startle, result in myoclonic spikes. On the basis of the electroencephalographic findings, Lennox suggested that stimulating activities may be of therapeutic value in petit mal epilepsy. We have found that barbiturates are exceedingly effective in abolishing myoclonic waves and twitches. There can be little doubt from the foregoing observations of the opposite character of petit mal and myoclonic epilepsy.

Gibbs [16] speculated on a "spectrum" of cortical frequencies as an aid to interpretation of the electroencephalogram. The long wavelengths, or slow waves, are correlated with surgical anesthesia, stupor, sleep and other conditions associated with low levels of consciousness. The shorter wavelengths are correlated with attention, fright, confusion or ether and alcohol excitement. He enunciated the concept that expenditure of energy in the normal cerebral cortex is indicated by the reciprocal relation of frequency and amplitude. During attention the 10 per second alpha waves are replaced by small rapid beta waves, 25 or more per second. This is, according to Gibbs, an indication that the cortex is using a maximal supply of energy. When both frequency and amplitude are increased an abnormal use of energy occurs, and a grand mal seizure results. In both petit mal and grand mal epilepsy the upswing or abnormal use of energy is associated with a combination of large waves and few rapid spikes, which are replaced by spikes during the clonic phase, when the downswing appears at the end of the seizure. There is thus a swing from the slow end of the spectrum and back again—a typical biologic equilibrating mechanism following stimulation. In myoclonic epilepsy the swing seems to begin from the fast

16. Gibbs, F. A.: Interpretations of the Electroencephalogram, J. Psychol. **4**: 365, 1937.

end of the spectrum, beginning with frequent large slow waves with gradually increasing bursts of spikes.

Simultaneous leads from the occiput and the frontal region leave no doubt that the myoclonic attack is built up from the frontal region and radiates over the brain posteriorly before it culminates in a major seizure. The flat curve of exhaustion was not seen in one instance in which a spontaneous seizure was not preceded by increasing spikes (fig. 2*B*). Instead, large slow waves appeared, as in the tracings taken in the intervals. These large slow waves are possibly related to the organic degenerative changes in the cortical cells. They are similar to the large slow waves seen in sleep, although, as Lennox stated, a comparison of epilepsy and sleep advances knowledge but little.

Simultaneous muscle and cortical leads showed congruity in time between the spikes and the myoclonic twitchings. A hypothalamic or basal lead taken simultaneously by a method recently described [17] showed almost similar spike configuration, important in that the basal lead showed a latent period of three-tenths second. This is of interest in that since the pathologic feature of myoclonic epilepsy, i. e., intracellular amyloid bodies, is most intense in the dentate nucleus and the basal ganglia, myoclonus has been accepted as of basilar origin. For example, Hodskins and Yakolev expressed the belief that it is subcortical epilepsy and an amyostatic syndrome. It may be recalled that Friedreich and Unverricht concluded that myoclonus originates in the cells of the anterior horn. Our electroencephalographic evidence indicates that the discharge has its primary focus in the frontal lobes.

Over the concepts applied to the epilepsies the explosive theory has held sway. The sudden, excessive motor discharge has been presumed to have its concomitant in the brain in a sudden nervous discharge or excitation or, according to others, in a sudden release of lower centers from higher control. Numerous causes for such catastrophic changes in neural excitability have been postulated—from short circuiting over scar tissue to, as has been most widely accepted, vascular spasm caused by general changes in the acid-base equilibrium or lack of oxygen or causing in itself local metabolic changes in the nerve tissue.

Electroencephalographic studies have greatly altered ideas concerning the genesis of the epilepsies. The studies of Lennox, Gibbs and others seem to show that the epilepsies are accompaniments of disturbances in rhythm of electrical discharges within the brain. An epileptic attack seems to be a manifestation of the breakdown of individual rhythms of portions of the cerebral cortex and fusion of these rhythms into one, so that the cortex discharges as a whole. The rate-regulating

17. Grinker, R. R.: A Method for Studying and Influencing Cortico-Hypothalamic Relations, Science **87**:73, 1938.

mechanism is disturbed. The result is an explosive discharge, but its evolution is by no means sudden. Long before the attack occurs evidences of alterations in the normal cortical rhythm are visible in the electroencephalogram.

Myoclonic epilepsy affords an unusual opportunity to study the "building-up" process preceding an attack, since this process is gradual and cumulative, requiring several days for its completion, and its dissipation is abrupt, with the crescendo-like development of a generalized convulsion. Most important of all, however, the electrical manifestations of the "building up" to a major attack are directly mirrored in the clinical symptoms easily visible in the form of myoclonic jerks. From the clinical and laboratory studies which we have presented, there is little doubt that the epileptic attack is not a sudden explosion arising from a sudden metabolic or vascular, or even psychic, catastrophe. It is gradually developed and comes as a climax to a series of prodromes of disturbances in cortical rhythm. Therefore, explanations for the final epileptic discharge must include considerations of the early initial alterations of rhythm.

One cannot generalize from myoclonic epilepsy to the other epilepsies, for, as will be seen, they differ even electrically, although petit mal and myoclonia are probably variations in opposite directions of a common nucleus, seen in its purest form in grand mal seizures. We suggest, however, that myoclonia is a homologue of continuous or intermittent prodromes sometimes evident, but often obscured, in other types of epilepsy. A feeling of malaise, irritability, depression, and the like, is masked clinically, whereas myoclonia is obvious. Electroencephalographic tracings of prodromes in the psychic sphere may show evidences of a "building-up" process similar to that in the myoclonic prodromes. This, of necessity, would be convincing evidence that in other epilepsies as well the seizure is not a sudden catastrophe but an end result of a crescendo-like alteration in rhythm, perhaps self precipitating.

EXPERIMENTAL STUDY OF MACULAR REPRESENTATION IN THE MONKEY

G. L. MAISON, M.D.*
ST. LOUIS

P. SETTLAGE, PH.D.
CHICAGO
AND
W. F. GRETHER, M.S.
NEW HAVEN, CONN.

Two theories have been defended in the pages of the ARCHIVES to explain the difference between the macula-sparing and the macula-splitting hemianopias found in man after interruption of the optic radiation. One theory, championed by Penfield, Evans and MacMillan,[1] holds that certain macular fibers in each optic radiation pass, or send collateral branches which pass, through the splenium of the corpus callosum to the contralateral occipital cortex. According to this view, a lesion interrupting the optic radiation before these decussating fibers leave it results in macula-splitting hemianopia, whereas a lesion posterior to that point results in macula-sparing hemianopia.

The other theory, held by Fox and German,[2] interprets the clinical findings according to the postulate that the macula is diffusely represented throughout in the striate cortex. Thus, a lesion in the temporal lobe may result in macula-splitting hemianopia because all macular fibers in the optic radiation on one side have been interrupted. On the other hand, the usual occipital lobectomy results in macular sparing because, according to this theory, the most anterior portion of the striate cortex has been left intact.

---

* The Department of Physiology, the St. Louis University School of Medicine.
From the Departments of Psychology and Physiology, the University of Wisconsin.

This work was carried out in the Wisconsin Primate Laboratory, with the cooperation of Dr. H. F. Harlow, of the Department of Psychology, and was financed in part by a grant from the research budget of the University of Wisconsin for the year 1936-1937.

1. Penfield, W.; Evans, J. P., and MacMillan, J. A.: Visual Pathways in Man with Particular Reference to Macular Representation, Arch. Neurol. & Psychiat. **33**:816 (April) 1935.

2. Fox, J. C., Jr., and German, W. J.: Macular Vision Following Cerebral Resection, Arch. Neurol. & Psychiat. **35**:808 (April) 1936.

If a case could be found in which the optic tract had been sectioned on one side and the contralateral occipital lobe removed, no cortical vision should be observed unless macular fibers or their collateral branches cross to the opposite occipital cortex. If a remnant of cortical vision existed, the theoretic pathway of impulses would be through the uncut optic tract, the splenium and thence to the remaining occipital lobe. Since such a case is unlikely to occur clinically, it was decided to attempt production of the lesion in the monkey, the visual system of which is similar to that of man.

Differentiation of cortical and subcortical vision in the monkey was accomplished by Klüver.[3] He showed that after bilateral occipital lobectomy the monkey can make no visual discriminations except those of differences in brightness. Object vision, perception of color and spatial arrangements and the like are abolished. It can fairly be assumed that retention of the slightest degree of macular vision would be accompanied by behavioral manifestations of a higher order of visual capacity than that shown by cortically blind animals.[4] Hence, our preparation should be functionally equivalent to the cortically blind preparation if bilateral macular representation does not exist; it should have demonstrably superior visual capacity if representation is bilateral.

METHOD

Mature Macacus rhesus monkeys were subjected to unilateral occipital lobectomy when under anesthesia induced by intravenous injection of barbiturates. All tissue posterior to a coronal section through the hemisphere at the level of the external parieto-occipital (simian) sulcus was removed. In a second stage, after an interval of four months, with the animals under similar anesthesia, the optic tract on the contralateral side was sectioned. A high mortality resulted with any approach, but the best results were obtained when a subtemporal approach was employed. It was usually necessary to remove a little more than 1 cm. of the anteroinferior pole of the temporal lobe in order to reveal the region of the sella turcica. The tract was sectioned just posterior to the chiasm by tension on a silk ligature, which was threaded under the tract on an aneurysm needle.

After the second operation each animal was carefully observed for signs of object vision over a period of several months. Reactions to food offered to the animal and avoidance of obstacles were carefully noted. In addition, 1 animal was tested for crude brightness discrimination. The apparatus consisted chiefly of two chains attached to receptacles for food. The chain attached to the loaded

3. Klüver, H.: An Analysis of the Effects of the Removal of the Occipital Lobes in Monkeys, J. Psychol. **2**:49, 1936.

4. Of the 3 monkeys studied by Klüver, the striate cortex was completely removed in 1 animal, whereas the most anterior portions escaped removal in the other two; yet the visual ability of all 3 animals was of the same type. It thus seems that retention of a slight amount of "peripheral cortex" is insufficient for the mediation of any discriminations except those based solely on the amount of luminous flux entering the eyes. These data argue against the existence of diffuse macular representation in the monkey.

food box turned on an electric lamp when pulled; pulling the chain attached to the empty box caused no change in illumination. By testing each chain with a short pull, the animal could differentiate the receptacle which contained food. The pupillary light reflex was also tested.

After several months had been allowed for recovery from the operation and adequate observations had been made, the animals were killed and the brains fixed in formaldehyde. The presence or absence of degenerative changes in the optic tracts was determined by sectioning and staining with iron hematoxylin.

RESULTS

Two complete preparations were obtained in ten attempts. In both these animals the left optic tract was cut and the right occipital lobe removed.

Neither of the completed preparations showed any sign of object vision. There was no ability to avoid unfamiliar objects. Though the animal was ravenously hungry, no ability to locate food was ever observed in any part of the visual field. No response was obtained to silent threatening gestures, though unusual noises made the animal markedly apprehensive.

The animal tested for crude brightness discrimination reacted selectively to the brightness of a 3.8 volt flashlight bulb at a distance of 2 feet (60.9 cm.) when a resistance of 17 ohms was connected in series and 2.5 volts was applied. This degree of discrimination was not as high as that obtained by Klüver in his cortically blind preparations, nor did it represent the greatest capacity of our animal. No attempt was made to obtain liminal discriminations of brightness differences. Extended efforts to obtain discriminations based on the position of the light source, whether to the right or to the left of the cage front, did not result in any differential responses.

The response of the pupils to diffuse light was normal in both animals. No attempt was made to elicit the Wernicke phenomenon.

In each case the left optic tract showed massive degeneration of fibers, whereas the right optic tract revealed no degenerative changes.

COMMENT

The retention of brightness vision and the pupillary reflex in the 2 preparations, as well as the results of histologic examination, proves that one optic tract remained partially or wholly intact. The complete loss of object vision in the animals must, therefore, be attributed to total interruption of the optic radiations from the lateral geniculate body of the side on which the tract was normal. This finding allows two interpretations with regard to the decussation of macular fibers in the splenium of Macacus rhesus monkeys.

1. *Interruption by Occipital Lobectomy of Macular Fibers Before Decussation.*—The validity of this conclusion is doubtful, since comparable lesions in man result in macular sparing. Therefore, if such fibers exist they probably lie well anterior to the plane of the section for lobectomy.

2. *Absence of Decussation of Macular Fibers in Rhesus Monkeys.*—If the fibers exist and were left intact, a fraction of macular vision should have been retained by the animals.

The second conclusion is supported by the studies of Poljak [5] who observed no degeneration in the contralateral geniculate body after destruction of the macular cortex in monkeys. His observations, however, do not obviate the possibility that collateral branches arise from the macular fibers in the visual radiation to pass to the contralateral cortex by way of the splenium. Failure to find object vision in our preparation rules out both direct fibers and collateral branches if, as seems reasonable, these leave the main path of the optic radiation anterior to the level of the section.

That no crossed pathway exists in the monkey does not prove that it is not present in man, though such a conclusion is strongly suggested. It is not known at present whether macular sparing and macular splitting occur in the monkey as they do in man; if they do, the evidence is against decussation of fibers in the splenium as the mechanism. The blindness in our preparation also shows that there is no macular cortex anterior to the level of the external parieto-occipital sulcus in the monkey.

SUMMARY AND CONCLUSIONS

1. No vision except very crude brightness perception was present in 2 monkeys after section of one optic tract just behind the chiasm and removal of the contralateral occipital lobe.

2. Absence of form vision in this preparation virtually rules out the crossing of macular radiation fibers or their collateral branches through the splenium to the contralateral occipital cortex in the Macacus rhesus monkey.

---

5. Poljak, S.: Projection of the Retina upon the Cerebral Cortex, Based upon Experiments with Monkeys, A. Research Nerv. & Ment. Dis., Proc. **13**: 535, 1934.

SPECIAL ARTICLES

ANOXIA AND NEURAL METABOLISM

R. W. GERARD, M.D.
CHICAGO

If one may think of carbon as the basic element of organic structure, one may similarly look on oxygen as the basis of organic function. A considerable portion of the machinery of Metazoa is devoted to delivering an adequate supply of oxygen at the door of the individual cell, and the presence of special mechanisms (such as the carotid body) to insure the supply to the brain, as well as the prompt disturbance of neural function when oxygen is lacking, attests the special importance of oxygen for this organ. Neurons, like other body cells, require a continuous supply of energy for maintenance and action. This is obtained, in orthodox fashion, by oxidations with molecular oxygen in cell respiration and, to a lesser extent, by oxidations with organic molecules in the dismutations of glycolysis. Respiration of brain differs from that of muscle, so extensively studied as to be the tissue of reference, in at least two major points: It is quantitatively far more intense—the oxygen consumption per unit mass is about thirty times as rapid for gray matter as for muscle or peripheral nerve—and it is qualitatively almost restricted to carbohydrates and their intermediates as substrates. It will be desirable to consider briefly these quantitative and qualitative aspects.

Oxidative energy is used by the resting cell to maintain the integrity of its structure and physicochemical organization. One specific use is to keep the surface membrane polarized, and it is readily demonstrated in nerve that the membrane potential falls progressively during anoxia.[1] One is tempted, therefore, to relate the high oxygen requirement of the brain to the peculiarly large surface of its extended branching cells; much effort has been devoted to an analysis of the oxygen used by the cell body, dendrites, axon and synapses. I cannot consider here (see another paper [2]) the bulk of this evidence, based on capillary richness in and measured respiration of various parts of the nervous system,

From the Department of Physiology, the University of Chicago.

Read as part of a symposium on "Anoxia" at the Federation of Biological Societies of America, March 30, 1938.

1. Gerard, R. W.: Am. J. Physiol. **92**:498, 1930.
2. Gerard, R. W.: A. Research Nerv. & Ment. Dis., Proc. **18**:316, 1938.

except to say that it is far from concordant and that each structure (except the axon, which, despite its large surface, certainly has a low metabolic rate, directly measurable in peripheral nerves) has been regarded by some investigators as especially responsible for the high respiratory rate of the brain. On the assumption that the rate of reduction of ferric chloride parallels that of the normal reduction of oxygen, Sugar and I have recently [3] obtained evidence of a high respiratory rate of the perikaryon and its processes with no indication of similar intensity at the synapses. (This, incidentally, speaks against the production of specific humoral agents by the synapsing structures.)

Aside from the problem of portions of the cell, there is considerable interest in the relative oxygen requirements of various regions of the brain, especially since some of the consequences of inadequate oxygen supply depend, presumably, on differential injury to structures the respiratory needs of which are greatest. In fact, the occurrence of degenerations in the globus pallidus, cornu ammonis and supragranular and granular layers of the cortex following periods of anoxia (e. g., clinically in cases of carbon monoxide or cyanide poisoning or of some psychoses) has been taken as evidence of their high metabolic rate. There is danger here of circular reasoning, and more direct evidence of oxygen requirements is needed. This is best obtained by measurements (1) of rates of respiration of isolated regions of the brain; (2) of related metabolic reactions or compounds; (3) of loss of function during anoxia (survival time), and (4) of later recovery in oxygen (revival time). The results from all sources are in reasonable agreement.

First, a word as to the absolute respiratory rate of the mammalian brain as a whole: This has been measured directly by the oxygen consumption of slices of brain in vitro or has been calculated from the arteriovenous difference in the oxygen content of the blood circulating in the intact brain and from the rate of blood flow. The values in vivo have steadily been twice or three times as great as those in vitro.[2] Brookens, Ectors and I,[4] by the use of a method permitting measurement, minute by minute, of the respiration of 1 or 2 mg. of the brain, have shown that the rate of respiration falls rapidly for a time after isolation and that the values in vivo are essentially correct. This fall, incidentally, is due mainly not to injury or exhausation of the substrate but to the absence of a heat-stable, dialyzable substance in the plasma

3. Sugar, O., and Gerard, R. W.: Am. J. Physiol. **123**:198, 1938. Gerard.[2]

4. Brookens, N. L.; Ectors, L., and Gerard, R. W.: Am. J. Physiol. **116**: 16, 1936.

(Shaffer, Chang and Gerard;[5] Alexander and Hastings[6]). It is yet to be proved how far differences in oxygen consumption, expressed as the number of cubic millimeters per hour per gram of fresh tissue, obtained by the Warburg method for different regions of the brain reflect the true rates; certainly, the absolute values on record, rate of oxygen consumption about 2,000 cu. mm., are far below the correct value of 5,000 cu. mm.

Despite this limitation, Dixon and Meyer[7] found by the usual respirometer technic a higher rate of oxygen consumption for the cerebellar cortex than for the cerebrum and a high value for the cornu ammonis as well. It is interesting that the cerebellum also has the richest content of ascorbic acid[8] and of the stimulating potassium ion.[9] Miss Panimon and I (unpublished data) found the respiratory rate of the medulla of the guinea pig hardly a third as high as that of the cerebrum. From such data one might expect the cornu ammonis to be relatively sensitive to anoxia and the medulla distinctly resistant.

After a sudden stoppage of the oxygen supply neurons lose the ability to function after a variable interval (survival time). This depends on: (1) the amount of oxygen or oxidizing reserve still available; (2) the rate of use of energy by the cell—ordinarily, its metabolic rate—and (3) the extent to which other reactions, such as glycolysis, can supply the needed energy. For mammalian nerve, oxidizing reserves in the axons and energy derived from glycolysis and creatine-phosphate splitting can maintain conduction at body temperature for about twenty minutes.[1] If an amount of oxidized glutathione equal to the total content of the brain (3 millimols[10]) were present, it would require over five minutes to reduce it alone. (Frog nerve at 20 C. uses one-fifth as much oxygen as mammalian nerve and contains 0.33 millimol of glutathione.[11]) The human brain ceases to function, as indicated by fainting, well within twenty seconds after the flow of blood through it is suddenly stopped.[12] Other things being equal, this suggests a rate of respiration about sixty times that of nerve, which is probably nearly correct for the active brain. Surely, no great oxidizing reserve is present in the cells, though

5. Shaffer, M.; Chang, T. H., and Gerard, R. W.: Am. J. Physiol. **111**: 697, 1935.

6. Alexander, B., and Hastings, A. B.: Proc. Soc. Exper. Biol. & Med. **37**:268, 1937.

7. Dixon, T. F., and Meyer, A.: Biochem. J. **30**:1577, 1936.

8. Gerard, R. W., in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1937, vol. 6, p. 419.

9. Tupikova, N., and Gerard, R. W.: Am. J. Physiol. **119**:414, 1937.

10. Binet, L., and Weller, G.: Bull. Soc. chim. biol. **18**:358, 1936.

11. Nicoll, P. A.: Am. J. Physiol. **119**:593, 1937.

12. Weiss, S., and Baker, J. P.: Medicine **12**:297, 1933.

the oxygen in the capillary blood should last almost ten seconds, and glycolysis, which begins immediately,[13] does not long supply the needed energy.

More accurately, the survival time can be measured by the loss of electric potentials or the failure of synaptic transmission. Though transmission through the cervical sympathetic ganglion can resist almost an hour of anoxia,[14] neurons in the central nervous system become electrically quiescent in a few seconds after the sole artery left free is clamped. For the cat, under light anesthesia induced with pentobarbital sodium, after carotid occlusion produced by ligation of one carotid and both vertebral arteries, some characteristic survival times are: motor cortex, fifteen seconds; corona radiata, twenty seconds; optic thalamus (geniculate body), from fifteen to thirty seconds, and cerebellum, ten seconds. In the medulla bursts continue for fifty seconds. Incidentally, high frequency potentials fall out much before slow ones (Sugar and Gerard [14a]).

A second chronometric index is that of duration of complete anoxia after which revival with oxygen is still possible, the revival time. Since this is a measure of the rate at which irreversible cell changes, due to proteolysis, accumulation of acid and the like, occur it need have no relation to the respiratory rate or survival time. Actually, however, it seems to run fairly parallel. Thus, the cortex can survive only five minutes of anoxia, while the medulla survives twenty minutes or more [15] (respiratory rate of the cortex is three times that of the medulla). Also frog nerve at 20 C. has a respiratory rate one-two hundred and fiftieth that of mammalian cortex at 37 C. and a revival time of over fifteen hours, about two hundred times that of brain.[2]

A third measure, the time of recovery or the interval between readmission of oxygen (after varying periods of anoxia) and return of function, has been little studied. For the cat's brain my colleagues and I have obtained values of from two to twenty seconds in different locations after from thirty to one hundred and twenty seconds of anoxia. (The time of recovery increases with the duration of anoxia.)

Turning from the regional oxygen requirements to those common to all neurons, if not to cells in general, one may ask: First, what cell mechanisms determine the rate of oxygen use, and, second, how does oxygen consumption or pressure, in turn, control other reaction rates? Respiration of brain and nerve is independent of the oxygen pressure

13. Kerr, S. E., and Ghantus, M. L.: J. Biol. Chem. **117**:217, 1937.

14. Bronk, D. W., and Larrabee, M. G.: Am. J. Physiol. **119**:279, 1937.

14a. Sugar, O., and Gerard, R. W.: J. Neurophysiol, to be published.

15. Heymans, C.; Bouckaert, J. J.; Jourdan, F.; Nowak, S. J. G., and Farber, S.: Survival and Revival of Nerve Centers Following Acute Anemia, Arch. Neurol. & Psychiat. **38**:304 (Aug.) 1937.

over a wide range above and below the normal level and almost as completely of the concentration of the substrate.[16] In an isolated succinoxidase system, oxidation of succinic acid follows the monomolecular equation,[17] and many steps in the decomposition of carbohydrates have been shown to be reversible and to follow the law of mass action. Yet in the less simple system obtained merely by cytolyzing brain in water, the initial rate at which sodium succinate is oxidized is almost independent of its concentration,[18] as was shown earlier for oxidation of lactates by bacteria.[19] In intact cells the failure of the simple relations of mass action is most evident.

If the velocity of reaction is not controlled by reactant (or end product) concentrations, it must depend on the activity of the catalytic systems or the physical availability to each other of interacting molecules. Since constant resting rates can be increased abruptly many times by stimuli which set cells in function, it follows that there is present catalyst in unavailable form (chemically inactive or physically obstructed) which can rapidly be mobilized. A new extensive synthesis of enzyme molecules seems too much to expect in a fraction of a second. Thus, Rubenstein and Gerard [20] as well as Runnström,[21] interpreted the quantitative and qualitative changes in respiration which accompany fertilization of eggs of the sea urchin in terms of structural breakdown and improved contact of substrates and catalysts. Korr [22] has recently presented further evidence indicating that on fertilization it is cytochrome, previously held inactive in colloidal micelles, which becomes free and active. This accounts, for example, for the insensitivity to cyanide of respiration during the resting stage and the sensitivity of the increased respiration after fertilization. For brain, it has been shown that the oxidase-cytochrome system does not limit the rate of oxidation, which depends on the dehydrases or their immediately related carriers. At least, administration of thyroid, which increases the respiration of rat brain a third or more, markedly augments in vitro the oxidation of dextrose and its metabolic intermediates but not that of other substances, with no comparable increase in the activity of the paraphenylenediamine-oxidizing system.[23]

16. Gerard, R. W., in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, Long Island, N. Y., The Biological Laboratory, 1936, vol. 4, p. 194.

17. Stotz, E., and Hastings, A. B.: J. Biol. Chem. **118**:479, 1937.

18. Cohen, M. B., and Gerard, R. W.: Am. J. Physiol. **119**:34, 1937.

19. Gerard, R. W.: Biol. Bull. **60**:227, 1931.

20. Rubenstein, B. B., and Gerard, R. W.: J. Gen. Physiol. **17**:677, 1934.

21. Runnström, J.: Protoplasma **10**:106, 1930.

22. Korr, I. M.: J. Cell. & Comp. Physiol. **10**:461, 1937.

23. Cohen, R. A., and Gerard, R. W.: J. Cell. & Comp. Physiol. **10**:223, 1937.

However, if oxygen has little influence on the rate of oxidation, it has a profound effect on the velocity, even direction, of other metabolic events in the cell. Complete anoxia initiates proteolytic and other destructive processes which end in cell death. According to Rosenbohm,[24] even 30 mg. of lactic acid per hundred grams of tissue can initiate proteolysis in the brain in the absence of oxygen. It has also been the accepted belief that glycolysis is released only in proportion to the actual respiratory loss—the quantitative Pasteur-Meyerhof relationship. This relation seems to have broken down in both directions. I refer not to the various dyes, salts and drugs which initiate aerobic glycolysis without decreasing respiration, and which perhaps act by blocking a coupling mechanism or enzyme,[25] but to simple changes in oxygen pressure. Thus, Kempner [26] showed for various individual cells that the rate of respiration may be markedly diminished at low oxygen tension (e. g., loss of 60 per cent at an oxygen tension of 4 per cent), while glycolysis begins only on still further lowering of oxygen pressure. Conversely, for the rat retina Laser [27] found that with diminishing oxygen tension glycolysis appears long before any alteration in respiration. Thus, oxygen pressure rather than the rate of oxygen consumption seems to control glycolysis. Further, both Kempner and Laser found a low respiratory quotient at low oxygen tension.

It does not seem true, as Dickens and Simer [28] urged, that only carbohydrate oxidation suppresses glycolysis. This objection is based partly on the facts previously mentioned and partly on the finding of Holmes, Gerard and Solomon [29] that in isolated rabbit nerve sugar no longer decreases after a few hours, though normal respiration continues and glycolysis remains in abeyance. Further, an appropriate dose of iodoacetate decreases glycolysis in the brain without attacking the oxidation of dextrose [30] whereas nicotine [31] and sodium hydroxymalonate [32] interfere with oxidation of lactates, again leaving that of dextrose intact. There is undoubtedly, however, an especially intimate relation between the oxidation and the fermentation of dextrose, and the brain, with its almost exclusive use of dextrose as fuel, offers excellent material on which to study this.

---

24. Rosenbohm, A.: Biochem. Ztschr. **289**:279, 1936.
25. Dickens, F.: Biochem. J. **30**:1233, 1936.
26. Kempner, W.: J. Cell. & Comp. Physiol. **10**:339, 1937.
27. Laser, H.: Biochem. J. **31**:1671 and 1677, 1937.
28. Dickens, R., and Simer, F.: Biochem. J. **25**:975, 1931.
29. Holmes, E. G.; Gerard, R. W., and Solomon, E. I.: Am. J. Physiol. **93**:342, 1930.
30. Shorr, E. S.; Barbeer, B., and Malam, M.: Science **87**:168, 1938.
31. Baker, Z., and Himwich, H. E.: Am. J. Physiol. **123**:6, 1938.
32. Jowett, M., and Quastel, J. H.: Biochem. J. **31**:275, 1937.

In such a case, the rate of utilization of dextrose is the sum of the molecules changed to lactic acid and of those burned. This sum increases with lowered oxygen tension if glycolysis appears before oxygen consumption is decreased, or even in the classic Pasteur relation, in which three times as much sugar is fermented anaerobically as is oxidized in air. Of course, with very low respiratory quotients at low oxygen pressures, some of the sugar started into the metabolic hopper does not come through, and one must consider the accumulation of partially oxidized intermediate substances. This is actually not a simple problem, since the present picture calls for no transfer of hydrogen or electrons through cytochrome and its oxidase except at the first and last steps of dextrose catabolism; a discussion, however, would lead too far for present consideration.

The problem of control of the rate of utilization of dextrose by oxygen resolves itself into two groups of possibilities. Either oxygen removes by further oxidation some intermediate substance which otherwise would react to form lactic acid—pyruvic acid could play this role, since it is reduced anaerobically in the brain, as in the Embden-Meyerhof sequence,[33] or is oxidized in oxygen, possibly over C_4 acid stages[34] (see Peters[35] and Jowett and Quastel[32] for difficulties with this scheme)—or (2) it removes or inactivates a catalyst. Since lack of oxygen increases the total number of dextrose molecules attacked, the latter possibility seems more likely. Further, if the dehydrase-carrier components of the system limit respiration, as they do, these must be activated by anoxia,[36] since the early steps of oxidation and fermentation of dextrose seem to be the same.

Whether lack of oxygen acts by increasing the ratio of active —SH to inactive —S-S— forms of an essential enzyme, as urged by Michaelis and Runnström,[37] or by releasing bound substrate or catalyst by partial disintegration of structure[38] or in other ways cannot yet be answered. It seems probable, however, that it acts by controlling catalytic activity, since diminished oxygen pressure increases the breakdown of sugar molecules and does so with no change in the actual number of oxygen molecules reacting in the system (CO, but not CN —, may produce the same changes[27]). Further, the ability of dyes, which play the role of

33. Page, I. H.: Chemistry of the Brain, Springfield, Ill., Charles C. Thomas, Publisher, 1937, chap. 6.

34. Lipmann, F.: Skandinav. Arch. f. Physiol. **76**:255, 1937. Weil-Malherbe, H.: Biochem. J. **31**:299, 1937. Krebs, H., and Johnson, W. A.: ibid. **31**:645, 1937.

35. Peters, R. A.: Acta brev. Neerland. **7**:1, 1937.

36. Gerard, R. W., and Falk, I. S.: Biol. Bull. **60**:213, 1931.

37. Michaelis, L., and Runnström, J.: Proc. Soc. Exper. Biol. & Med. **32**: 343, 1934.

38. Dixon, K. C., and Holmes, E. G.: Nature, London **135**:995, 1935.

carriers, to initiate aerobic glycolysis while even increasing respiration [39] exemplifies such a catalytic action.

This discussion has led to consideration of the qualitative aspects of brain metabolism. Under a large variety of conditions the respiratory quotient of brain remains clearly at 1.[40] Except under severe insulin action,[41] the glycogen content remains constant, but dextrose as the only added substrate can support brain respiration in vitro.[42] In vivo dextrose is removed by the brain from the blood passing through it. Interestingly, both in man without anesthesia and in the dog when under anesthesia induced with ether or a barbiturate, about twice as much sugar disappears from the blood to enter the brain as could be oxidized by the oxygen removed simultaneously.[2] Even in the isolated nerve of the bull frog a similar excessive loss of dextrose occurs.[29] It is hard to guess the fate of this extra amount, if it occurs under conditions of real equilibrium, unless a nonreducing intermediate of sugar metabolism is continually passing back into the blood. In any event, it is clear from the foregoing and much similar evidence that dextrose itself is the preferred, and under normal conditions possibly the only, fuel of the brain.

This brings hypoglycemia into peculiarly close relation to hypoxemia, for if either substrate or oxygen is deficient metabolism must be interfered with. Indeed, the prediction has been confirmed in man [43] and the dog [44] and mouse [45] that a lowered supply of dextrose to the brain decreases its oxygen consumption. The synergic effects of a decrease in dextrose and in oxygen described by Glickman and Gellhorn [46] require more elaborate discussion than time permits. It thus appears that some effects of hypoglycemia, at least, are related to anoxia or, conversely, that anoxia acts by interfering with dextrose metabolism. (The parallel stimulation of orthosympathetic centers by hypoglycemia and asphyxia has long been emphasized by Cannon.[47])

One cannot go thus far in a consideration of brain metabolism today without meeting the burning question of dementia praecox and

39. Gerard, R. W.: Am. J. Physiol. **97**:523, 1931.

40. Himwich, H. E., and Nahum, L. H.: Proc. Soc. Exper. Biol. & Med. **26**:496, 1929. Dickens, F.: Biochem. J. **30**:661, 1936.

41. Kerr, S. E., and Ghantus, M. L.: J. Biol. Chem. **116**:9, 1936.

42. Loebel, R. O.: Biochem. Ztschr. **161**:219, 1925. Sherif, M., and Holmes, E. G.: Biochem. J. **24**:400, 1930.

43. Dameshek, W., and Myerson, M.: Insulin Hypoglycemia: Mechanism of Neurologic Symptoms, Arch. Neurol & Psychiat. **33**:1 (Jan.) 1935.

44. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Science **86**:271, 1937.

45. Holmes, E. G.: Biochem. J. **24**:914, 1930.

46. Glickman, N., and Gellhorn, E.: Am. J. Physiol. **121**:358, 1938.

47. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, ed. 2, New York, D. Appleton and Company, 1929.

its current empiric treatments. Sakel, who introduced insulin therapy, concocted a theoretic interpretation, of which Cobb [48] accurately said:

> Such a naive mixture of physics, chemistry, physiology and circumlocution has rarely appeared in a medical journal. It is scientific hypothesis degenerating to mixed metaphor!

Insulin shock obviously interferes with oxidations in the brain, and the intensity of neurologic symptoms parallels the glycogen content of the brain far more closely than the sugar content of the blood.[41] That oxidation is disturbed is apparent from intense cyanosis during the spastic phase of a metrazol convulsion and has been proved chemically by Himwich.[49] Thyroid, also reported to be effective in therapy in sufficient doses, increases the rate of respiration and the use of sugar in the brain.[23] The narcotic *Dauerschlaf*, considered useful in treating some psychoses, has been shown [50] to disturb the oxidation of sugar by the brain, especially the change of lactic to pyruvic acid. Even the well established treatment of dementia paralytica with hyperthermia may well depend on altered dextrose, metabolism of the brain, since Dixon [51] found a release of aerobic glycolysis and injury to respiration at temperatures in the upper range of induced fever.

Whether or not schizophrenia is a consequence of chronic hypoxia of the brain, it seems that the therapeutic agents so far effective have in common an action on the oxidation of sugar by the brain. I am aware that the term "schizophrenia" covers a multitude of disease entities and that symptoms in individual cases may be induced immediately mainly either by psychic or by physical factors. In one group, at least, there are distinct physiologic changes in neural function which can be duplicated in man and animals by interference with oxidations in the brain, e. g., catatonia,[52] or which are prima facie evidence of lowered brain metabolism, e. g., low basal metabolic rate and insensitiveness to thyroid.[53] (Whether in addition to, or even underlying, the disturbances in oxidation there are irregularities of the autonomic nervous system, inadequacies of circulation and the like is beyond the scope of this discussion.)

This brings me to a final point for consideration. How does the metabolism of the cell control its physiologic function, or, more

48. Cobb, S.: Review of Neuropsychiatry for 1937, Arch. Int. Med. **60**:1098 (Dec.) 1937.

49. Himwich, H. E.; Bowman, K. M.; Fazekas, J. F., and Orenstein, L. L.: Proc. Soc. Exper. Biol. & Med. **37**:359, 1937.

50. Jowett, M., and Quastel, J. H.: Biochem. J. **31**:565, 1937.

51. Dixon, K. C.: Biochem. J. **30**:1483, 1936.

52. Jongbloed, J.: Arch. néerl. de physiol. **19**:538, 1934.

53. (*a*) Gjessing, R.: Arch. f. Psychiat. **96**:319, 1932; **104**:355, 1936. (*b*) Hoskins, R. G.: Oxygen Metabolism in Schizophrenia, Arch. Neurol. & Psychiat. **38**:1261 (Dec.) 1937.

particularly for the present discussion, how does anoxia affect neuron activity? Asphyxial convulsions and the hyperkinesis of partial anoxia are well known; furthermore, cyanide, narcotics, and insulin lead to excessive motor discharges before paralysis. These, however, may represent phenomena due to successive depression of regions of the brain from above down and release of lower neurons rather than transient overactivity of individual neurons due to their own metabolic defect. The action potentials of the brain may perhaps be relied on for a more certain answer, and many investigators have made such studies.[54]

Holding the breath increases and overventilation slows the frequency of brain potentials in man, but these effects are related most immediately to changes in carbon dioxide. In the cat or frog sudden stoppage of blood flow (or exclusion of oxygen from the bathing solution in vitro) often increases the rate and amplitude before the loss of activity previously described. After anoxia there is regularly a period of discharge of large high frequency waves and frequently brain potentials remain more marked (often with spindles or periodic bursts) for a long time after the period of anoxia. This recalls the marked overshooting of the total action potentials of nerve after a stay in nitrogen [1] and the similar burst of increased oxygen consumption.[55] Cyanide, likewise, causes brain potentials to pass through a phase of rapid discharge.[56] Hoagland,[57] and also Lennox [54d] found that hypoglycemia in man slows cortical potential rhythms, but in cats Dubner and I [54e] observed that fast waves may appear in the geniculate body under the action of insulin and, particularly, that afferent stimuli give excessive, repetitive and prolonged responses in potential—all of which effects are promptly abolished by intravenous injection of dextrose. Under the action of iodoacetate, also, rapid and peculiarly large, complex potentials develop in the frog's brain as glycolysis is interfered with, and lactic acid, which is burned, eliminates these effects.[56] It seems reasonable to conclude that either during the early stages of decreased oxidation or after the episode there is stimulation of neurons; furthermore, there is basis for the

54. (*a*) Gibbs, F. A.; Davis, H., and Lennox, W. G.: Electroencephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133 (Dec.) 1935. (*b*) Bremer, F., and Thomas, J.: Compt. rend. Soc. de biol. **123**:1256 and 1261, 1936. (*c*) Lindsley, D. B., and Rubenstein, B. B.: Proc. Soc. Exper. Biol. & Med. **35**:558, 1937. (*d*) Lennox, W. G.: A. Research Nerv. & Ment. Dis., Proc., 1938, vol. 18. (*e*) Dubner, H., and Gerard, R. W.: Am. J. Physiol. **123**:56, 1938; in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, Long Island, N. Y., The Biological Laboratory, 1936, vol. 4, p. 292.

55. Gerard, R. W.: Am. J. Physiol. **82**:381, 1927.

56. Libet, B., and Gerard, R. W.: Am. J. Physiol. **123**:128, 1938.

57. Hoagland, H.; Rubin, M. A., and Cameron, D. E.: Am. J. Physiol. **120**: 559, 1937.

view that a relatively long period of increased respiration and activity may follow one of interference with metabolism. This may depend on a leakage of potassium ions from the interior of the neuron during anoxia, for which there is some evidence,[58] and it is well established that a moderate increase in external potassium ions is a powerful stimulus to activity.[59]

One may, then, rationalize the various current therapies for schizophrenia in terms of an increase in the respiration of the brain induced directly or on the rebound. This is most evident in the work of Gjessing,[53a] and now of Hoskins,[53b] showing that patients with dementia praecox are unusually resistant to thyroid but are improved by its use in sufficiently high doses. In view of the fact that thyroid increases the dehydrase systems of the brain [23] and of the large body of work, initiated by Barron,[60] on the carrier action of dyes, I suggested several years ago that these substances may increase respiration in the brain in vivo, as they do in vitro,[61] and be useful in the therapy of dementia praecox, at least the catatonic form. With the cooperation since the spring of 1936 of Dr. Esther B. Tietz, of the Longview State Hospital, Cincinnati, and of Dr. H. D. Singer and his staff at the Illinois Research Hospitals, it has been possible to test the action of pyocyanine, methylthionine chloride U. S. P. (methylene blue) and thionine on schizophrenic patients. The results, with pyocyanine especially, have been sufficiently encouraging to warrant more extensive experimentation.

SUMMARY

Respiration of the brain is about thirty times as intense as that of muscle or nerve. Since energy is used by the resting cell to maintain cell surface, this high rate of respiration may be related to the branching of neurons. A histochemical method fails to demonstrate the expected rapid reduction by synapses and neuropil. The comparative oxygen needs of gross structures of the brain are indicated by direct measurements of respiration in vitro, by concentration of reactants and by the time required for loss of function during and recovery after anoxia. The cerebellar cortex has the most intense rate of respiration, and other masses of the brain form a consistent series.

The respiratory rate is ordinarily determined not by the concentration of oxygen or of substrate but by enzyme activity. Enzyme concen-

58. Gerard, R. W., and Tupikova, N.: Unpublished data.

59. Gerard, R. W., and Magoun, H. W.: Proc. Soc. Exper. Biol. & Med. **34**:755, 1936.

60. Barron, E. S. G.: J. Biol. Chem. **81**:445, 1929.

61. Chang, T. H., and Gerard, R. W.: Proc. Soc. Exper. Biol. & Med. **27**:1073, 1930; Am. J. Physiol. **97**:511, 1931. Young, L.: J. Biol. Chem. **120**:659, 1937.

tration can be increased slowly by feeding thyroid, but the more sudden increases in respiration on passing from rest to activity depend on release of bound or inactive enzyme.

Oxygen tension, rather than oxygen use, controls the rate at which sugar is glycolyzed to lactic acid; the relation of oxidation to fermentation of dextrose is discussed, as well as the mechanisms in the brain for carrying out both these important metabolic processes.

The normal substrate for brain is dextrose, and more of this leaves the blood than could be burned by the oxygen obtained simultaneously. Hypoglycemia, therefore, acts much like hypoxia on function of the brain. Interference with oxidation in the brain leads to a secondary "overshooting" with increased activity, related perhaps to liberation of potassium.

Several empiric therapies for dementia praecox or other psychoses—insulin shock, metrazol, thyroid, *Dauerschlaf* and hyperthermia—directly or indirectly increase the oxidation of sugar by the brain. Dyes likewise stimulate respiration in the brain, and the results of tests of their therapeutic action, especially that of pyocyanine in treatment of schizophrenia, have been encouraging.

Case Reports

MENINGIOMA OF THE LATERAL VENTRICLE

Report of Two Cases

J. G. Lyerly, M. D., Jacksonville, Fla.

Meningioma of the lateral ventricle is sufficiently rare to justify the report of 2 cases that have occurred recently in my practice. In each instance the tumor was a firm, encapsulated growth occurring in one of the lateral ventricles and attached to the choroid plexus, from which it seemed to arise. The symptoms were typical of those of increased intracranial pressure as seen in cases of tumor of the brain in which there are no localizing signs to warrant exploration without ventriculographic examination. The tumor can be removed completely with little difficulty by means of modern neurosurgical technic, leaving the patient with little or no impairment.

Only a few cases have been reported in the literature. Cushing [1] mentioned a case in which he performed operation in 1916; the patient made a good recovery and is now living twenty years later. Fincher [2] reported 2 cases, in 1 of which operation was performed by Dowman and in the other by him. Petit-Dutaillis and Bertrand [3] reported a case in which the tumor was removed after resection of the occipital lobe. Roscher [4] reported a case in which the tumor arose from the choroid plexus of the right ventricle and the patient died shortly after partial removal of the growth. De Busscher [5] reported a case in which the diagnosis was confirmed by autopsy after an unsuccessful operation.

In my 2 cases, as well as in the cases reported in the literature, the tumor appeared to arise from the choroid plexus. An explanation for this may be had when one considers that the choroid plexus may carry with it remnants of the pia-arachnoid in its development from the neural crest. These latent meningeal cells may be the source of the tumor later in life. Meningiomas of this type are similar in pathologic pattern and appearance to meningiomas occurring on the surface of the brain. Calcification and psammoma bodies are sometimes observed

Read at a meeting of the Harvey Cushing Society, Philadelphia, May 7, 1937.

1. Cushing, H.: Studies in Intracranial Physiology and Surgery, New York, Oxford University Press, 1926; personal communication to the author.

2. Fincher, E. F.: Intraventricular Tumors of the Cerebrum, South. M. J. **27**:667-676 (Aug.) 1934.

3. Petit-Dutaillis, D., and Bertrand, I.: Fibroblastome profond intracérébral de l'hémisphère gauche, sans connexions méningées décalables. Ablation de la tumeur. Guérison opératoire, Rev. neurol. **39**:96-100 (July) 1932.

4. Roscher, F.: Meningiomas with Report of Intracerebral Tumor Belonging to Group of Meningiomas, Acta path. et microbiol. Scandinav. **10**:288-303, 1933.

5. de Busscher, J.: Ueber das intraventrikuläire Meningiom des rechten Hinterhorns, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**: 522-529, 1935.

in the ventricular growth, but in neither of the 2 cases reported here was this true. In both my cases pathologic studies revealed numerous fibroglial and collagenous fibers, as are seen in the fibroblastic type of meningioma.

It is interesting to note that all the cases reported occurred in women. In my 2 cases the duration of symptoms was about one year, and in both instances they followed almost immediately termination of pregnancy at term.

REPORT OF CASES

CASE 1.—*Meningioma of the left lateral ventricle; operation and removal; recovery.*

Mrs. J. C., aged 23, referred by Dr. Stanley Erwin, of Jacksonville, Fla., was admitted to St. Luke's Hospital of that city, on March 13, 1935, with the chief complaint of headache. The family history was without significance. The patient

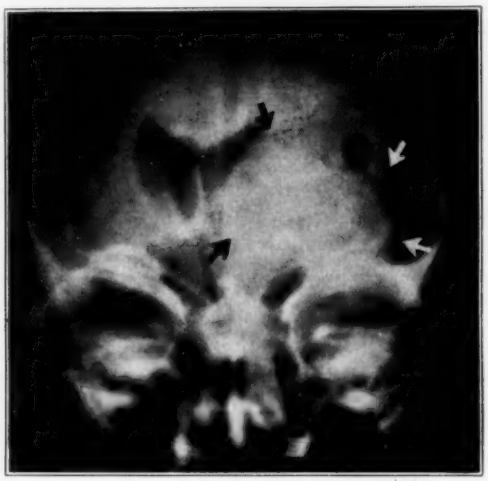


Fig. 1 (case 1).—Ventriculogram showing the anteroposterior view. The left ventricle is filled with the tumor. The ventricular system is shifted to the right.

had been told that she had diabetes when 4 years of age, which lasted one year. The tonsils were removed four months before admission. She had had one child, born by breech delivery, who died two hours after birth. The menstrual history was normal.

The present illness began in April 1934, one month after the birth of the child, with headache in the early morning hours, located mostly in the right frontal region. With the headache there were dizziness and a tendency to stagger to the right. Projectile vomiting had been present for four months. There was blurred vision with periods of almost complete blindness. The usual weight was 200 pounds (90.7 Kg.); it was now 150 pounds (68 Kg.). There was no history of polyuria or polydipsia. There were no attacks of unconsciousness or convulsions.

Examination.—The patient was of large frame. The blood pressure was 114 systolic and 68 diastolic, and general physical examination revealed nothing abnormal.

The head was normal except for a short scar in the right frontal region resulting, according to the history, from injury with forceps at birth. The right side of the head was more tender to percussion than the left.

Neurologic Examination.—Cranial Nerves: Smell was normal; visual acuity was 10/16 in the right eye and 10/30 in the left. The eyegrounds showed choked disks, of 4 diopters, in both eyes, with considerable pallor of the left. The pupillary reactions and movements of the eyes were normal. Sensibility of the face was normal. There was no facial weakness. Hearing was good in both ears, but the patient complained of tinnitus in both ears and deafness in the right. The gag reflex, the sternocleidomastoid muscles and protrusion of the tongue were normal.

Lobes of the Brain: There was no impairment of memory, euphoria or change in personality. The patient was right handed; there was no aphasia. No motor weakness or sensory loss could be demonstrated. There were no hallucina-

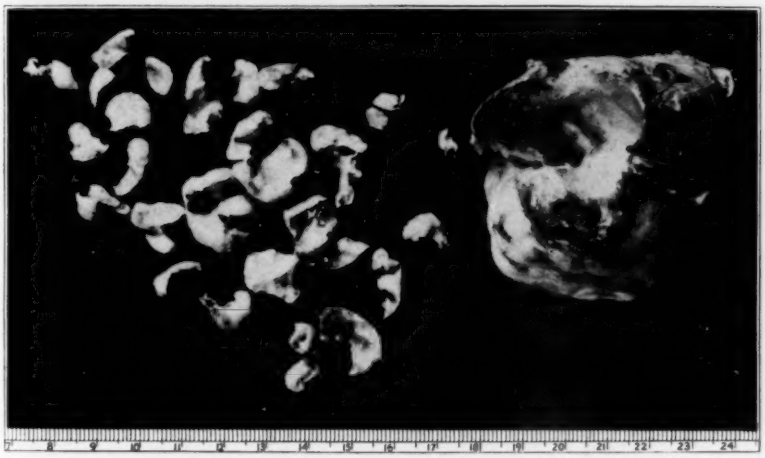


Fig. 2 (case 1).—Photograph of the tumor after removal. The tumor was reduced in size before the largest mass was completely removed.

tions of vision, smell or taste, and the visual fields were normal. There was no ataxia or adiadokokinesia. Nystagmus was not present. The Romberg sign was not elicited. Gait was normal.

Reflexes: Tendon jerks were present in both upper and lower extremities and equal on the two sides. There were no pathologic reflexes.

Other Procedures.—A roentgenogram of the skull was normal except for erosion of the dorsum sellae. The Kahn test of the blood and other laboratory examinations gave normal results.

Diagnosis.—The diagnosis was tumor of the brain, of uncertain localization. Ventriculographic examination was considered advisable.

Ventriculographic Examination (March 16).—No fluid was obtained from the left ventricle; the right could be filled with air. The ventriculogram showed shifting of the right ventricle, the interventricular septum and the third ventricle to the right, with marked filling deformity of the left ventricle, suggesting an intraventricular tumor (fig. 1).

Operation.—A left osteoplastic flap was turned down on the same day. There was greatly increased cerebral pressure, with flattening of the convolutions. On exploration with a ventricular needle, definite resistance, resembling that of fibrous tissue, was met at a depth of 4 cm. in various places throughout the operative field. A transcortical incision was made through the posteroparietal region down to the tumor. The tumor was firm, fibrous and encapsulated. A piece of tumor was removed for microscopic examination. Because of the large size of the tumor and in order to obtain further information as to the pathologic type, it was decided to close the wound and complete the operation at a second stage.

Second Stage of Operation (March 23): The wound was reopened and the tumor exposed. The growth was reduced in size by removal of pieces with the

Fig. 3 (case 1).—Photomicrograph showing the fibroblastic type of the meningioma.

electrosurgical loop. After it was reduced sufficiently to be delivered through the operative opening in the parietal lobe, the remaining large piece was removed without difficulty (fig. 2). Nowhere was it adherent to the brain or to any portion of the ventricular wall other than the choroid plexus. Bleeding from several large vessels running from the choroid plexus to the tumor was controlled without difficulty.

Pathologic Report (Dr. L. Y. Dyrenforth).—The specimen consisted of a roughly spheroid, firm, gray mass, 6 cm. in diameter, with many smaller pieces of similar tissue. It was fairly smooth and tough to the knife. The interior was homogeneous and dense. The weight of the tumor was 100 Gm.

Microscopic Examination.—The microscopic picture was that of nearly acellular, fibrous connective tissue, interspersed here and there with leukocytes of inflammatory type and fibrocytes. Small areas of hemorrhage occurred at one edge, and there were a few large blood vessels having no demonstrable endothelial lining. There was evidence of a thin capsule over one portion (fig. 3).

Diagnosis.—The diagnosis was meningioma, of fibroblastic type.

Progress.—After the operation there were considerable night hemiparesis and aphasia. Aphasia was not complete, as the patient was able to say a few words and understanding was fairly good. There was delay in healing of the wound due to sloughing of the margin at the posterior limb of the incision. Occasional spinal drainage was necessary to control intracranial pressure during the next two weeks and to prevent separation of the wound. The patient was out of bed and walking at the time of discharge from the hospital, on June 1. There was considerable weakness of the right arm and leg, but she was able to walk with a limp on the right. Speech was considerably impaired, but she was able to make her wants known. About one year after operation she had two generalized convulsions a few hours apart, which have not recurred. There have been no

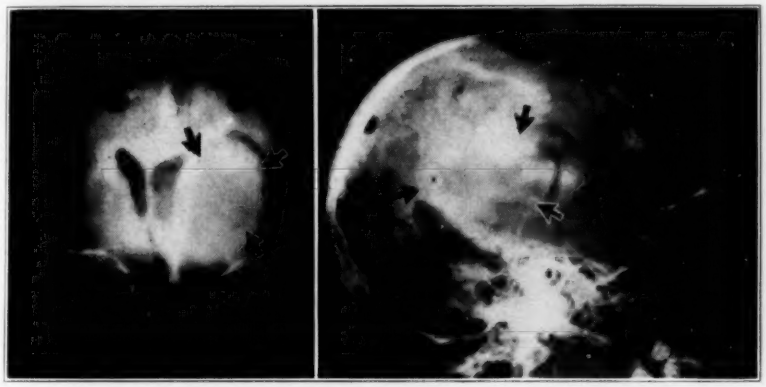


Fig. 4 (case 2).—Ventriculogram showing the round tumor situated in the posterior part of the lateral ventricle. A thin shadow of air surrounding the tumor can be seen in the anteroposterior view.

signs of recurrence of the growth, and the present impairment consists of partial aphasia and some weakness of the right arm and leg. She is able to take walks and help with the housework.

While this patient had pronounced symptoms of generalized intracranial pressure, there were no localizing signs, in spite of the large tissue mass, more than 6 cm. in diameter, in the left lateral ventricle. It probably would have been better to have completed the operation in one stage and to have reduced the size of the tumor during its removal in order to minimize injury of the overlying brain. While there is some physical impairment, the patient is cheerful, comfortable and well pleased with the result.

CASE 2.—*Meningioma of the right lateral ventricle. Operative removal; recovery.*

Mrs. P. B. J., aged 28, was admitted to St. Vincent's Hospital, Jacksonville, Fla., on May 4, 1936, having been referred by Dr. C. D. Christ, of Orlando, with the chief complaint of headache and double vision. The family history was of no importance. The past history was irrelevant, with no history of injury to the

head. The menstrual history was normal. The patient had 1 child, 1 year of age; she had had no other pregnancies.

The present illness began one year before, one month after the birth of the child, with headache which was mostly generalized. The headache was usually worse in the morning; for the past month it had been worse on the right side. There had been nausea and frequently projectile vomiting during the past three

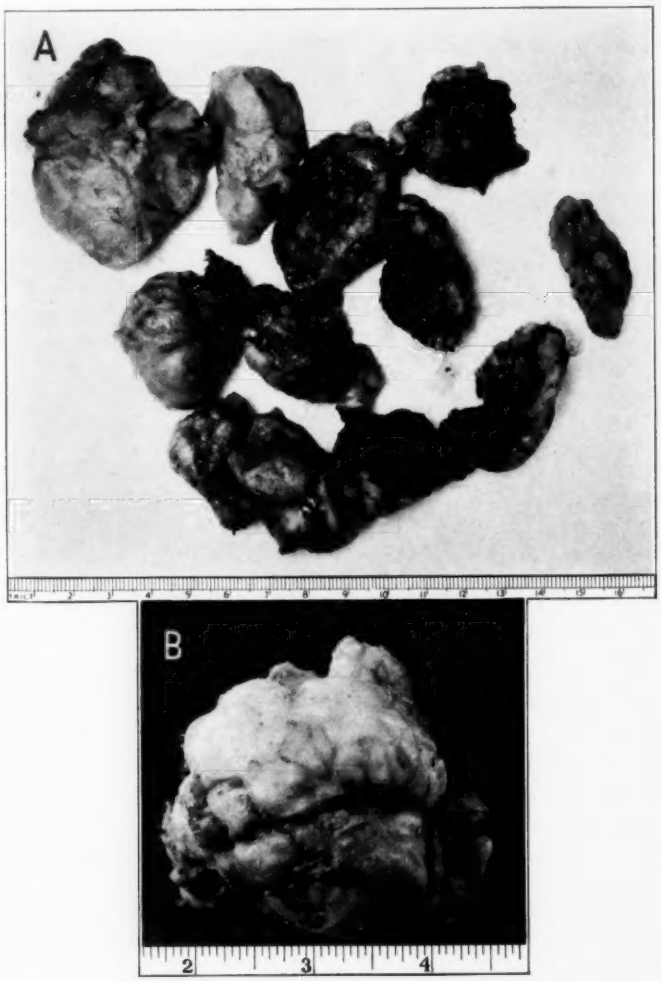


Fig. 5 (case 2).—*A*, photograph of the tumor, showing the size of the individual pieces removed to reduce its size. *B*, pieces of the tumor shown in *A* assembled as the original tumor.

months. Slight dizziness was associated with the headache. There had been no convulsions. The patient had had a sensation of numbness on the right side of the face for the past six months. There had been no numbness or weakness of the extremities. Recently, she had smelled bad odors.

Examination.—The patient was fairly well nourished and developed. General physical examination revealed nothing abnormal; the blood pressure was 120 systolic and 60 diastolic. The head presented no localized tenderness or abnormalities.

Neurologic Examination.—Cranial Nerves: Smell was normal. There were choked disks of 2 diopters, bilaterally. Visual acuity was 10/15 in each eye. The pupils were equal, and the reaction was normal. There was slight weakness of the right external rectus muscle, with diplopia. Sensation of the face and cornea was normal. There was no facial weakness. Hearing was good in both ears; there was a history of tinnitus in the right. The cranial nerves were otherwise normal.

Lobes of the Brain: There was considerable tremor of the left hand, but no motor weakness could be demonstrated on either side. Sensation was normal.

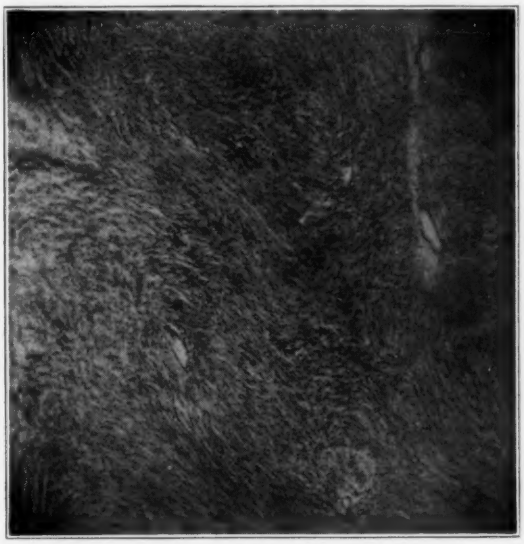


Fig. 6 (case 2).—Photomicrograph showing the fibroblastic type of the meningioma.

There was partial homonymous hemianopia on the left. The tendon jerks were equal on the two sides, with no pathologic reflexes.

Laboratory Examination.—Urinalysis and complete examination of the blood, including the Kahn test, gave normal results.

Diagnosis.—The diagnosis was tumor of the brain, probably in the right temporal lobe; however, ventriculographic examination was deemed advisable.

Ventriculographic Examination (May 6).—On insertion into the right occipitoparietal region, the needle met resistance like that of a fibrous tissue mass, and no fluid was obtained from the right ventricle. The left ventricle was filled with air. The ventriculogram showed marked displacement of the ventricular system to the left. A thin shadow of air appeared to surround a large round mass in the right lateral ventricle (fig. 4).

Operation.—On May 6 an osteoplastic flap was turned down on the right side. There was considerable increase in intradural pressure, with flattening of

the convolutions. On insertion of the ventricular needle, the tumor was encountered at a depth of 2 cm. throughout the operative field. A vertical incision was made through the posteroparietal region to the tumor. The growth was encapsulated, round and firm and measured about 7 cm. in diameter. The tumor was incised with the electrosurgical knife, and sections were removed with little bleeding (fig. 5 *A* and *B*). The growth was removed completely in sections through a relatively small opening in the brain. There were several large vessels running from the tumor to the choroid plexus. Bleeding from these vessels was easily controlled, chiefly by electrocoagulation. The growth was nowhere adherent to the ventricular walls and was situated entirely within the ventricle.

Pathologic Report (Dr. C. E. Royce).—The specimen consisted of several irregular pieces, weighing altogether 100 Gm. The surface contours were nodular, and the color was light yellowish gray. The consistency was firm, and the structure seemed to be fibrous. The central areas on section showed patches of dark red.

Microscopic Examination.—Sections showed bundles of fibers arranged in whorls. The cellular picture ranged from groups of spindle-shaped cells with large nuclei to areas which were almost acellular. Blood vessels were not numerous; they were small and had very thin walls. No mitoses were seen (fig. 6).

Diagnosis.—The diagnosis was meningioma, of fibroblastic type.

Progress.—On May 7 it was noticed that there was considerable weakness of the left side of the face and the left arm and leg; within a few days this was disappearing, and weakness on the left side could scarcely be noticed on the patient's discharge from the hospital, on May 25. There was no difficulty in speech or other complication. The pressure symptoms had subsided, and the patient was walking at the time of discharge. A recent communication stated that she had remained well, with no physical or mental impairment.

Comment.—Although the tumor in this case was as large as that in the first, it could be removed completely in one stage and through a small opening by cutting it into sections. As a result, the patient had little impairment after the operation. Paralysis had disappeared by the time she was discharged from the hospital. The visual fields have not been checked since she left the hospital, as she has moved to a distant state and recent communications have been by letter.

SUMMARY

These 2 cases are reported because of the rarity in the lateral ventricle of this type of tumor. Instead of indicating a dural origin, as Cushing stated, these cases further confirm the theory that the tumor arises from the pia-arachnoid portion of the meninges, the remnants of which are sometimes seen in the choroid plexus. In each case the tumor was removed successfully at operation, and the patient made a good recovery; in the first case, however, there have remained slight hemiparesis and partial aphasia, but not to the point of complete disability. There was nothing in the history or clinical examination in either case to indicate the type or accurate location of the lesion, but the ventriculographic findings were conclusive. In each case the tumor was situated posteriorly and simply expanded the ventricle, without producing obstructive hydrocephalus from blockage of the foramen of Monro.

Dr. Louise Eisenhardt, New Haven, Conn., assisted in the pathologic examination of these tumors.

EPENDYMAL CYST OF THE CERVICODORSAL REGION OF THE SPINAL CORD

IRVING HYMAN, M.D.; WALLACE B. HAMBY, M.D., AND S. SANES, M.D., BUFFALO

A case is reported of an ependymal cyst on the anterior aspect of the cervicodorsal region of the spinal cord in a boy aged 7 years. Tumors of the spinal cord of any type are rare in children. One of us (W. B. H.)[1] in a review of the literature on tumors of the cord in children below the age of 15 years was able to find only 100 cases; in only 1 [2] of these was a cyst observed, and it was extradural. Other cases of extradural cysts in childhood have since been reported.[3] We have found no reference in the literature to a case similar to the one reported here.

REPORT OF A CASE

History.—An American boy aged 7, white, was referred to the Buffalo General Hospital on Jan. 9, 1936, by Dr. Raymond W. Holt, of Niagara Falls, N. Y., because of pain in the cervical region of five months' duration. Since birth the left arm had been colder than the right and had appeared cyanotic. The patient otherwise was well until August 1935, when he began to complain of pain in the cervical region, with stiffness of the neck. The pain was intermittent and was exaggerated by moving the neck, so that the child carried the head forward and turned the neck only when necessary. Laughing, straining or coughing increased the pain severely and caused it to radiate about the left side of the neck, down the left arm and around the thorax, at the level of the first dorsal dermatome. There developed some weakness and atrophy of the left shoulder. A month prior to admission, the lower extremities had become weak; the patient walked with the knees partially flexed and within two weeks was unable to stand or to extend the knee joints completely.

Physical Examination.—The temperature was 100 F., the pulse rate 105 and the respiratory rate 25. The child was well developed and nourished and appeared intelligent. The pupils were equal and regular and reacted to light and in accommodation. The external ocular movements were normal. No abnormality of the ocular fundi was noted. The tonsils were large and hyperemic. The teeth were carious. A postnasal discharge was seen. Pain occurred with motion of the neck in any direction; it was most severe in the region of the sixth cervical vertebra. The lungs were clear and resonant throughout. The heart was of normal size; the tones were of good quality; the rate was regular, and no abnormal sounds were heard. The abdomen was soft. The penis showed slight phimosis.

From the Buffalo General Hospital and the University of Buffalo School of Medicine.

1. Hamby, W. B.: Tumors in the Spinal Canal in Childhood, J. Nerv. & Ment. Dis. **81**:24-42, 1935.

2. Collins, J., and Marks, H. E.: Early Diagnosis of Spinal Cord Tumor, Am. J. M. Sc. **149**:103-112, 1915.

3. Elsberg, C. A.; Dyke, C. G., and Brewer, E. D.: Tumors of the Spinal Cord, New York, Paul B. Hoeber, 1925, p. 322.

Neurologic Examination.—All movements of both arms were well performed, but the deltoid muscle appeared slightly smaller on the left side than on the right. The muscles of the neck were moderately rigid, particularly those of the posterior group, and the head was carried in an extended position. On rotation of the head to either side, a tremor developed in the shortened sternocleidomastoid muscle. On compression of the jugular vein, the child complained of pain in the left arm and around the thorax, in the distribution of the first dorsal dermatome. The left arm was colder than the right and was somewhat cyanotic. The radial pulses were equal. The biceps and triceps tendon reflexes were active and equal on the two

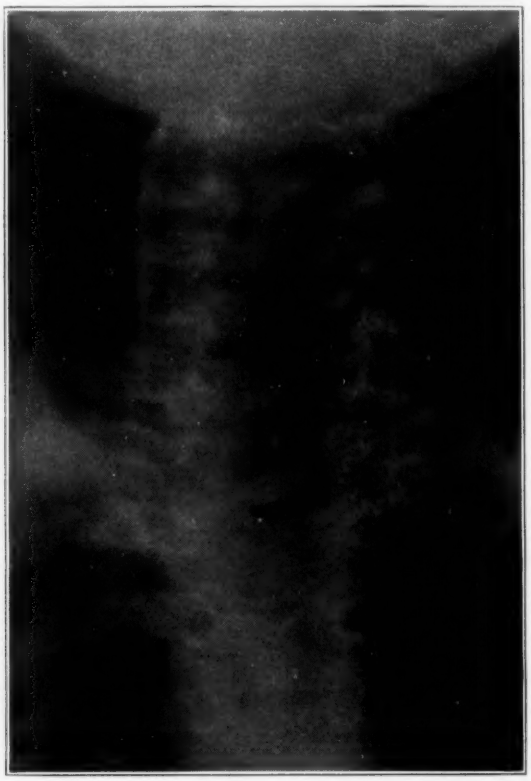


Fig. 1.—Roentgenogram of the cervical portion of the spine, showing dilatation of the bony canal, flattening of the pedicles and incomplete fusion of the laminas of the seventh cervical and first dorsal vertebrae.

sides. The abdominal reflexes were diminished on the left, and the left cremasteric reflex was absent. Both knees were flexed at an angle of 45 degrees. There was spasticity of both lower extremities, especially the right. The Babinski, Gordon, Chaddock and Oppenheim extensor toe reflexes and ankle clonus were present bilaterally. There was an indefinite disturbance in pain sense on the inner surface of the left thigh; sensation otherwise was normal.

Urinalysis and hematologic and blood chemical examinations revealed nothing abnormal.

Roentgenographic Examination (Dr. E. C. Koenig).—Roentgenographic examination of the cervical portion of the spine showed the entire bony canal to be dilated and the pedicles flattened and slightly concave. The widest point in the canal was at the first dorsal segment. The laminas of the seventh cervical vertebra were incompletely fused (fig. 1).

Lumbar Puncture.—The spinal fluid pressure was 100 mm. of water. The fluid was clear and slightly xanthochromic. No arterial pulsations were noted in the manometer, and there was no response to compression of the jugular veins.

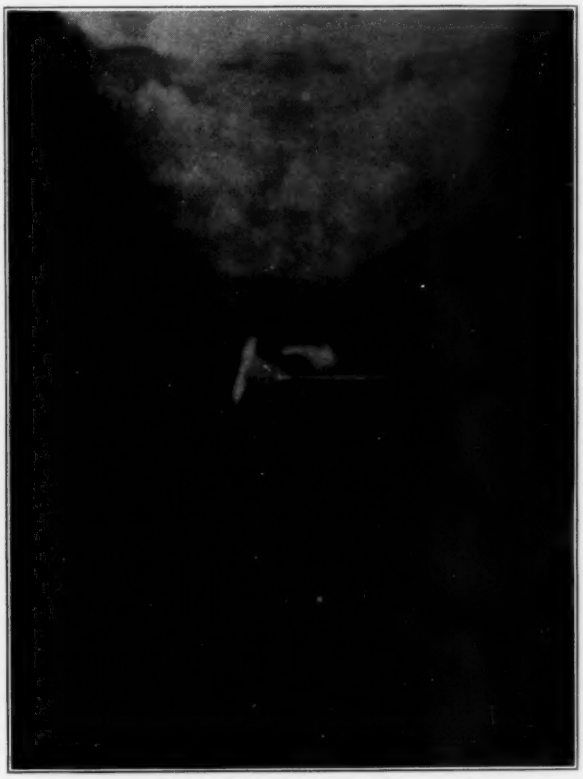


Fig. 2.—Roentgenogram taken after injection of iodized poppyseed oil, showing block at the level of the first dorsal vertebra.

The fluid contained 6 cells per cubic millimeter. Reactions to tests for globulin and albumin were 2 plus; reduction of copper was prompt.

On the following day, a combined cisternal and lumbar puncture was done. From the lumbar needle only a few drops of yellow fluid could be obtained, while clear fluid was removed from the cisterna magna. One cubic centimeter of iodized poppyseed oil was injected into the cistern, and 10 cc. of air, into the lumbar subarachnoid space. The needles were removed, and roentgenograms were made with the patient in the upright position. The air injected into the spine was not visualized. The iodized oil was seen to have descended to the level of the first

dorsal vertebra, where its descent was arrested; it appeared to "cap" a convex mass. A portion of the oil remained scattered along the cervical canal (fig. 2).

Preoperative Diagnosis.—The diagnosis was congenital tumor of the spinal cord at the first dorsal segment, with associated defects in the lower cervical vertebrae.

Operation.—On January 13, with the patient under anesthesia induced with avertin with amylene hydrate and nitrogen monoxide and in the sitting position, laminectomy was performed from the sixth cervical to the second dorsal vertebra, inclusive. The spinous processes and laminas of the seventh cervical and first dorsal vertebrae were incompletely formed. As the laminas were removed from

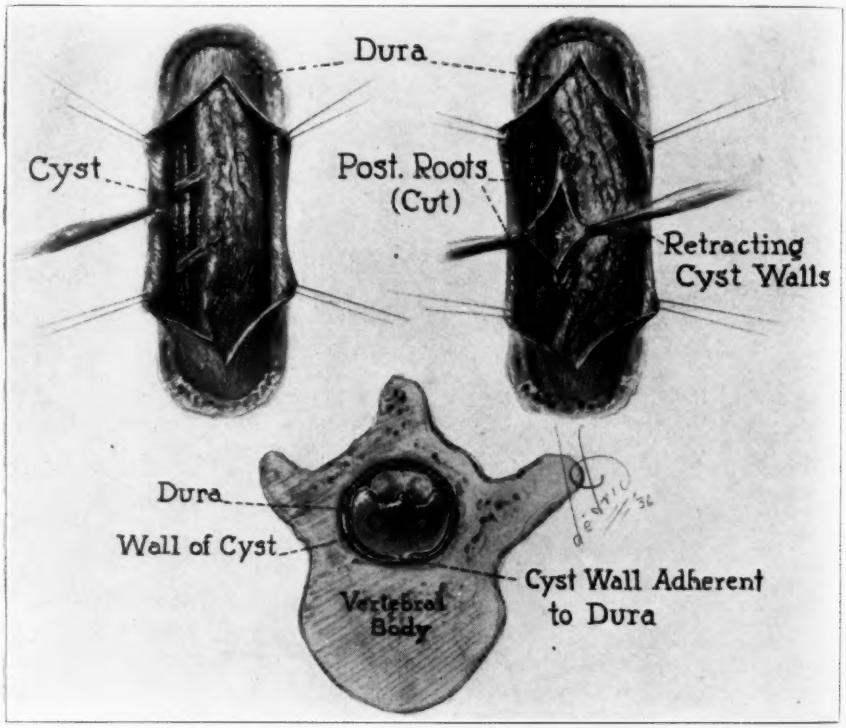


Fig. 3.—The upper drawings illustrate the gross changes seen at operation. The lower drawing represents a cross section of the cyst and cord. The vertebra shown, however, is of normal type.

below upward, the dura appeared to be displaced backward and did not pulsate until the lamina of the seventh cervical vertebra was removed. The dura was opened in the midline, and the cord was seen to be displaced backward by a mass in the anterior portion of the canal. The lesion resembled a cyst (fig. 3). A needle was introduced into the mass, and about 8 cc. of slightly cloudy fluid was removed. This relieved the block in the canal and allowed cerebrospinal fluid to flow downward from above the lesion; the entrapped iodized oil was expelled from the subarachnoid space. To allow mobility of the cord, the anterior and posterior roots of the first dorsal spinal nerve on the left were

severed, and the cord was displaced to the right by traction on the dentate ligament. The wall of the cyst was adherent to the dura anteriorly; section of the adhesion produced bleeding which was controlled by electrocoagulation. A line of cleavage between the wall of the cyst and the cord could not be seen. It was feared that radical removal of the cyst might result in damage to the cord, so only a portion of its wall was excised for study. After communication was established in the subarachnoid space above and below the lesion, the wound was closed.

Postoperative Course.—As soon as the patient awakened it was found that most of the spasticity of both lower extremities had disappeared and he was able to move the arms and legs without pain. On the third day after operation it was noticed that the patient exhibited a mild Horner syndrome; the left pupil

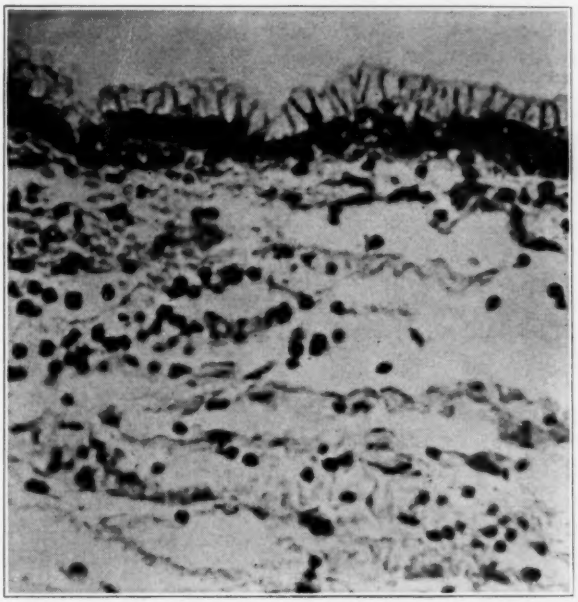


Fig. 4.—Section through the wall of the cyst, showing columnar epithelium and underlying connective tissue, with injection of capillaries, edema and cellular infiltration. Low power.

was smaller than the right, and the left lid drooped slightly. He gradually regained strength in the extremities and began to walk—at first with assistance and later unaided. He was able to extend the knees fully. At the time of discharge, on February 2, the knee jerks were hyperactive; the Babinski sign persisted on the left, and the left arm remained colder than the right and was definitely cyanotic.

Sixteen months later (May 29, 1937) the child was again examined. The pupils were round, regular and equal and reacted to light and in accommodation. No abnormality of the cranial nerves was found. The left hand was colder than the right, but less so than before. Cyanosis of the left upper extremity was less marked. Muscle strength was the same on the two sides and was apparently

normal. No atrophy of the shoulder muscles was noted. Sense of position in the toes was diminished. While no true Babinski response was elicited, the Chaddock, Oppenheim and Gordon extensor toe reflexes were present bilaterally. No Romberg sign or ankle clonus was obtained. Sensation for vibration, pain and temperature was normal.

Histologic Examination.—The tissue removed at operation was part of the thin wall of a cyst; demarcation between the lining and the underlying connective tissue was distinct.

The lining was well preserved and was epithelial, principally of simple type; often, however, it appeared pseudostratified. The lining cells were chiefly columnar. The cytoplasm which formed the peripheral two thirds of these cells took a basic stain and was foamy. In a few cells vacuoles were seen. Mucus was not demonstrated by thionin or mucicarmine stains. Because of fixation in formaldehyde and paraffin preparation, stains for fat and glycogen could not be employed. The nuclei of the columnar cells were located at the base, were ovoid or rectangular and lay either parallel with or perpendicular to the long axis of the cell. They stained diffusely dark blue, and some had light chromatin granules and nucleoli.

A number of the tall cells were wedge shaped; the base was slightly narrower than the free border. In places the lining cells were cuboid, with nuclei which occupied the whole length of the cell and produced a beaded appearance. Occasionally a single cell or a small group of successive cells showed long thin curved cilia; these could not be followed into the cellular cytoplasm. Rarely, basal bodies were observed between the cilia and the cell body. Slight papillary elevations were observed. Atypical cells or mitotic figures were not seen.

Beneath the epithelium the stroma was edematous and loose. It was infiltrated slightly with lymphocytes and neutrophils; the capillaries were engorged. There was recent hemorrhage. In its outer part the wall of collagenous tissue assumed a compact form.

The fluid removed from the cyst contained no cells; the reactions to tests for albumin and globulin were 4 plus, and a solution of copper was not reduced.

Histologic Diagnosis.—The histologic picture was that of the wall of an ependymal cyst (fig. 4).

COMMENT

Since the cyst in this case was associated with vasomotor changes, which had been present since birth, and with structural defects in the overlying bones, its origin must be sought in the embryonic development of the spinal cord. Its histologic structure was that of an ependymal derivative, the linings being of columnar and cuboid cells, some of which bore cilia. Its structure in no way suggested a pathogenetic relation to the meninges or blood vessels. At operation it was not possible to determine whether an anatomic connection existed between the cyst and the central canal of the cord; the cyst was inseparably attached to the ventral surface of the spinal cord. Elsberg [3] stated:

> In one instance, I have seen a dilatation and hernial protrusion of the central canal of the cord present the appearance of a cyst that compressed the cord. In this patient, the cyst was a part of an inflammatory lesion that affected both the cord itself and its membranes.

Such a lesion is not necessarily congenital, as was the cyst in our case.

The lesion in our case closely resembled cysts described as ependymal, vicinal to or associated with the cerebral ventricles. Ependymal cysts within the brain have been thought [4] to develop within rests of ependymal cells, resulting from evaginations of the ventricular lining into the brain substance. If the connecting stalk becomes obliterated the island of ependymal tissue may be left completely isolated from the ventricles. A similar explanation may account for the presence of an ependymal cyst on the anterior surface of the spinal cord, i. e., the possible evagination of the floor plate of the neural tube, with later isolation and cyst formation. Some factual substantiation can be offered for this possibility.

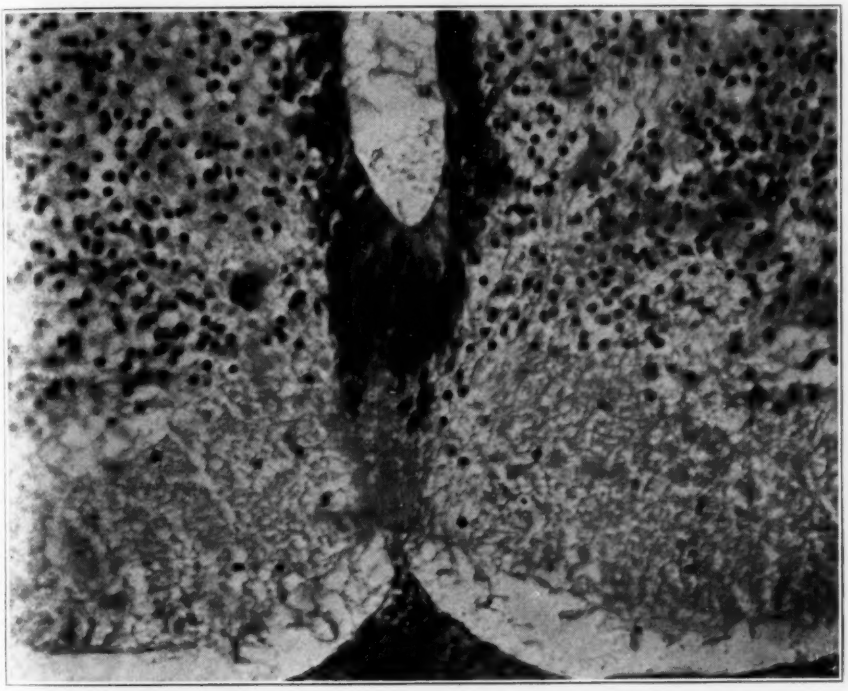


Fig. 5.—Section through the floor plate of the neural tube in a 22 mm. human embryo.

In the normal embryogenesis of the neural tube, after its separation from the rest of the ectoderm, the basal and alar plates become thick because of cellular proliferation and the differentiation of the primitive medullary epithelium into neurons and neuroglia cells, but the roof and floor plates remain thin. Of the two, the floor plate remains the more primitive. At certain stages in development these plates consist

4. Vitek, J.; Sachs, A., and Jedlička, V.: Subacute Compression of the Aqueduct of Sylvius by an Ependymal Cyst, Časop. lék. česk. **68**:1673 and 1730, 1929. Hamby, W. B., and Gardner, W. J.: An Ependymal Cyst in the Quadrigeminal Region, Arch. Neurol. & Psychiat. **33**:391-398 (Feb.) 1935.

essentially of a single layer of ependymal cells. Even when fully developed the plates are increased only slightly in thickness, although they become buried in the dorsal suture and the ventral fissure of the cord, respectively. Sections of a human embryo of 22 mm. which we examined showed this usual developmental condition (fig. 5); the floor plate was made up almost completely of ependymal cells. In view of this picture and the thinness of the floor plate, one may be tempted to postulate the pathogenesis of an ependymal cyst on the outer ventral surface of the spinal cord, isolated from the lining of the central canal, on the basis of localized isolation of ependymal cells of the floor plate with secondary cyst formation.

SUMMARY

The clinical, roentgenographic and pathologic observations are recorded in a case of an ependymal cyst of the cervicodorsal region of the spinal cord in a boy aged 7.

A possible explanation is offered for the occurrence of an ependymal cyst on the ventral aspect of the cord on the basis of localized isolation of cells of the floor plate of the neural tube, probably at an early stage of embryonic development.

Dr. K. L. Terplan, director of the pathologic laboratories of the Buffalo General Hospital and the University of Buffalo School of Medicine, and Dr. Wayne J. Atwell, professor of anatomy at the University of Buffalo School of Medicine, gave aid and criticism in preparation of the report of this case.

PITUITARY CACHEXIA (SIMMONDS' DISEASE)

Report of a Case with Autopsy

D. E. PLUMMER, M.D.
First Lieutenant, Medical Reserve Corps, U. S. Army
AND
J. RUDOLPH JAEGER, M.D.
Neurosurgeon, University of Colorado School of Medicine
DENVER

Our purpose in this paper is to present a case of a syndrome comparable to that described by Simmonds,[1] commonly known today as pituitary cachexia. Numerous cases have been reported in the European literature. Graham and Farquharson,[2] in 1931, reported the first cases in the American literature and stimulated an interest that has resulted in some important observations as to cause and therapy.

That the condition is caused by a disturbance of the normal function of the anterior lobe of the hypophysis is hardly to be doubted, but the pathologic conditions producing it are still somewhat confusing. Silver [3] reviewed the literature in 1933 and found 41 cases in which the diagnosis had been confirmed post mortem. He found various pathologic processes of the pituitary gland—atrophy, tumors, cysts, replacement by fibrous tissue, tuberculous caseation, necrosis, inflammatory processes, syphilitic lesions, degeneration and hematoma, which resulted in destruction of the functioning cells. The condition occurs more frequently in women, especially after repeated labor, when, according to Maresch,[4] it may be due to pituitary exhaustion. Transitory functional disorder of the gland has been suggested in some cases—a significant suggestion in view of the fact that remissions have been observed over a period of years. From a study of the literature it is evident that any one of a number of different pathologic conditions, either within the gland proper or in close proximity, may be the causative factor.

The clinical manifestations have been well summarized by Calder,[5] Hawkinson,[6] Weinstein [7] and others. Cases so far reported have been

1. Simmonds, M.: Ueber Hypophysisschwund mit tödlichen Ausgang, Deutsche med. Wchnschr. **40**:322, 1914.

2. Graham, D. A. L., and Farquharson, R. F.: Cases of Simmonds' Disease, abstracted, J. A. M. A. **96**:1987 (June 6) 1931.

3. Silver, S.: Simmonds' Disease (Cachexia Hypophyseopriva), Arch. Int. Med. **51**:175 (Feb.) 1933.

4. Maresch, R.: Zur Kenntnis der polyglandulären Erkrankungen, Verhandl. d. deutsch. path. Gesellsch. **17**:212, 1914.

5. Calder, R. M.: Pituitary Cachexia (Simmonds' Disease) Treated with Anterior Pituitary Extract, J. A. M. A. **98**:314 (Jan. 23) 1932.

(Footnotes continued on next page)

of far advanced disease, in which the diagnosis is not difficult. The question arises as to its existence in milder forms that may easily be mistaken for similar conditions. Patients making various complaints, such as loss of weight, loss of appetite, nervousness, insomnia, weakness and menstrual disorders, may deserve serious consideration of a possible pituitary source, especially since Costello [8] reported observing at autopsy what he called subclinical adenoma in the anterior lobe of the hypophysis in 22.5 per cent of a series of 1,000 unselected cases.

The case to be presented is typical in history and clinical findings; in addition, the neurologic findings make it evident that the condition was produced by some pressure-producing process in proximity to the pituitary gland.

REPORT OF CASE

The patient, a white man aged 22, was admitted to the hospital on March 18, 1936. His family and past history are irrelevant. He had reached his height of 6 feet (183 cm.) and weight of 185 pounds (84 Kg.) at the age of about 17. Eighteen months prior to admission he first noticed polyuria—from 4 to 6 liters of urine daily—and polydipsia. About six months later he noticed that he became fatigued easily and gradually lost appetite and considerable weight. There soon developed abdominal distress, nausea and vomiting after meals. About nine months after the onset he noticed slight blurring of vision and a constant occipital headache. He was a brunet, but a few months after the onset he noticed that his hair was turning light brown and his skin becoming lighter. The beard, the eyelashes, the eyebrows and the axillary and pubic hair became sparse as the disease progressed. The testes atrophied, and the patient gradually became impotent. The symptoms became progressively worse, and during the six weeks prior to admission he was confined to bed.

Examination.—The patient was 6 feet (183 cm.) tall and weighed 125 pounds (57 Kg.) (normal weight 185 pounds [84 Kg.]); he was extremely emaciated and weak, being unable to move himself in bed without assistance. He appeared considerably older than his 22 years. The skin had a slight yellowish color and was unusually dry, thin and slightly scaly. The hair was light brown, thinned, dry and brittle. The eyelashes, the eyebrows, the beard and the axillary and pubic hair were scanty. The teeth and the tonsils were grossly normal. The lymph glands and the thyroid were not palpable. The testes were markedly atrophied. The prostate gland had atrophied to such an extent that it could not be palpated. The pulse rate was 65 and weak. The blood pressure was 85 systolic and 60 diastolic. The heart was in normal position and of normal size. There was a soft systolic murmur at the apex. The lungs and the abdomen were normal.

---

6. Hawkinson, L. T.: Simmonds' Disease: Report of Case, J. A. M. A. **105**:20 (July 6) 1935.

7. Weinstein, A.: Multiglandular Syndromes Resembling Simmonds' Disease with Case Report, Am. J. M. Sc. **185**:245, 1935.

8. Costello, R. T.: Subclinical Adenomas of the Pituitary Body, Proc. Staff Meet., Mayo Clin. **10**:449 (July 17) 1935.

The right pupil was markedly dilated. Both pupils reacted sluggishly to light and in accommodation. Moderate bitemporal hemianopia was present. There was moderate atrophy of the optic nerve. The tendon reflexes were equal on the two sides but diminished. Muscular atrophy was prominent over the entire body.

The red blood cells numbered 5,543,000 and the leukocytes 6,150, with 57 per cent neutrophils, 34 per cent lymphocytes, 5 per cent monocytes and 4 per cent eosinophils. The twenty-four hour output of urine was 3,415 cc.; its analysis showed nothing abnormal other than low specific gravity. The Wassermann and the Kahn test gave negative results. The blood sugar was 97 mg. per hundred cubic centimeters. There was an increased tolerance of dextrose. The values for urea nitrogen and nonprotein nitrogen were normal. The calcium content of the blood was 10.3 mg. and the cholesterol content 156 mg. per hundred cubic centimeters. Gastric analysis showed moderate hypochlorhydria.

Roentgenologic examination of the skull, the chest and the long bones showed no abnormality. An electrocardiogram revealed nothing other than bradycardia and low voltage in all leads. The basal metabolic rate was —19 per cent. The spinal fluid had a normal pressure and contained 11 cells; there was a slight increase in globulin.

Diagnosis.—From the clinical observation a diagnosis of Simmonds' syndrome secondary to an intracranial tumor exerting pressure on the pituitary gland was justified. Surgical treatment was not considered advisable because of the poor condition of the patient.

Course.—In view of the favorable reports by Calder,[5] Hawkinson,[6] Striker,[9] Brougher[10] and others on the use of various extracts of the anterior lobe of the hypophysis, it was thought that by such medication the patient's condition might be improved sufficiently to allow him to withstand operation. He was given 200 rat units daily of gonadotropic substance from the urine of pregnant women. During the first month of this treatment the patient gained strength and weight (from 125 to 145 pounds [57 to 66 Kg.]) rapidly and became ambulatory. A recheck of the laboratory examinations showed no particular change. The basal metabolic rate decreased from —19 to —39 per cent.

In the second month of treatment the patient did not improve but began to retrogress and gradually lost 10 pounds (4.5 Kg.). There was, however, an increase in the size of the testes, and the patient had to shave frequently. During the third month of treatment the patient became progressively worse and was again confined to bed. Advanced atrophy of the optic nerve developed, and he gradually became totally blind. Rechecks of laboratory examinations showed no particular changes. Frequent roentgenologic examinations of the skull showed nothing suggestive of a pathologic condition.

The patient died on Oct. 2, 1936, and postmortem examination was done by Dr. Don Longfellow, of Fitzsimons General Hospital, United States Army, and Dr. Frank B. Queen, of the department of pathology, University of Colorado School of Medicine, twelve hours after death.

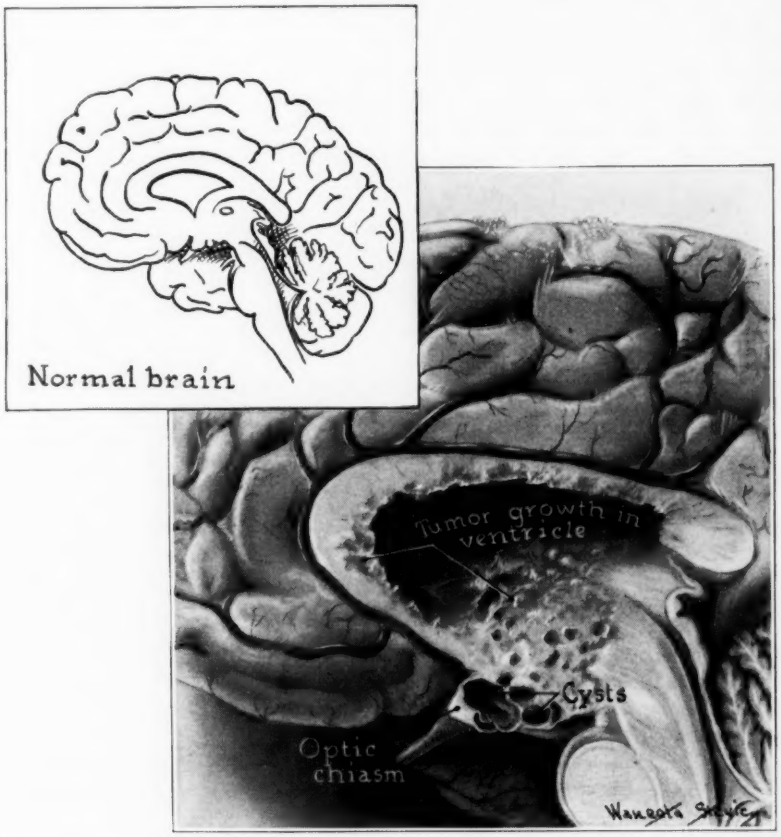
Autopsy.—The body weighed 110 pounds (50 Kg.). The pupils were round and unequal, the left measuring 3 mm. and the right 6 mm. in diameter. The conjunctivas and scleras were extremely pale. The superficial lymph nodes were not palpable. The external genitalia were markedly atrophied. The body hair was scant and of feminine distribution.

---

9. Striker, C.: A Case of Simmonds' Disease with Recovery, J. A. M. A. **101**:1994 (Dec. 16) 1933.

10. Brougher, J. C.: Simmonds' Disease: Case Report, Endocrinology **17**: 130, 1933.

The brain weighed 1,370 Gm. The optic chiasm was enlarged by a new growth, which had obliterated the normal anatomic markings. The mass was soft and ovoid and measured 3 by 22 cm. The infundibulum emerged from a point slightly posterior to the center of the mass and appeared to be of normal size. The region of the tuber cinereum was completely replaced by the mass. The pituitary gland appeared to be normal in size, and on section the surface showed nothing abnormal. The entire region of the hypothalamus on the right cerebral hemisphere consisted of cystic pale spongelike tissue. From this the tumor extended over the walls



Drawing illustrating location and extent of glioblastoma causing Simmonds' disease.

of the right lateral ventricle as far as could be seen without cutting of the ventricle. The whole body of the corpus callosum was involved on the right side. Nothing else of importance was noted.

The thyroid gland was extremely small. The sectioned surface was yellowish pink, waxy and translucent. No other important observations were made in the neck.

The lungs were normal. The condition of the heart was compatible with that in any chronic debilitating disease.

The liver appeared to be of normal size and was fairly firm and smooth. The sectioned surface was bloody, and the markings were indistinct. In the periphery of the right lobe were numerous small irregular yellowish mottled areas. The pancreas was small, weighing 7 Gm. Its sectioned surface was normal. The adrenal glands were small; section showed the cortices to be thin, with an apparent increase in medullary substance. The prostate gland was extremely small and soft. The sectioned surface was normal. The seminal vesicles were small but otherwise appeared normal. The testes were unusually small; the sectioned surfaces were shiny and homogeneous, and the tubules identified with difficulty. Nothing else of importance was seen in the abdomen.

Microscopic Examination.—The tumor in the brain was invasive, and in most areas its limits were poorly circumscribed. The cells of the tumor were of variable size, shape and appearance; the majority had dense large round nuclei, but in some the nucleus was vesicular and had a well defined nucleolus. There were many multinucleated cells. The cystic nature of the tumor noted grossly was not evident microscopically, but there were areas in which the stroma was loose, with large empty irregularly shaped spaces. The tumor was moderately vascular, but there was no perivascular concentration of the neoplastic cells. Mitotic figures were fairly frequent. Nothing remarkable was observed in uninvolved portions of the brain.

The section of the pituitary gland was distorted, and its normal architecture could not be made out. There was severe, widespread edema.

In the thyroid, the acini were filled with well stained colloid. The acinar epithelium was low, single layered and regular.

There was nothing remarkable in the heart and the lungs.

The liver showed nothing other than areas of infiltration of fat.

The pancreas showed the islands of Langerhans to be few, small and relatively acellular; the interacinar stroma was scant.

Advanced postmortem degeneration prevented a study of the adrenal glands.

The prostate had a dense fibromuscular stroma. Its glands were of normal appearance and number. There was no epithelial hyperplasia, and no corpora amylacea were seen.

The cellular detail of the testes was lost. The tunica was normal; the stroma was edematous, and there was active spermatogenesis.

The remainder of the microscopic examination revealed nothing noteworthy.

The pathologic diagnosis was glioblastoma multiforme of infiltrative type involving the tuber cinereum and adjacent structures.

COMMENT

The patient presented a rather typical clinical picture of Simmonds' syndrome. Pathologic examination revealed the presence of infiltrative new growth. Grossly, the pituitary gland was of normal size and shape. The microscopic changes in the gland were sufficient to account for the syndrome, although the gland was not invaded by the new growth. The pituitary gland was, no doubt, involved by pressure from adjacent structures and local irritation.

It appears from a study of the literature and of the present case that the successful treatment of the syndrome depends entirely on the patho-

logic process producing the condition. A sufficient number of cases have been reported in which the condition was due to new growth to justify the earliest possible diagnosis with a view to surgical removal. When an infectious process is encountered, treatment should be directed as specifically as possible to its eradication. When the process is degenerative, it appears that treatment should consist entirely of the use of anterior pituitary extracts or of the anterior pituitary-like gonadotropic principle of the urine of pregnant women.

It is of interest to note that the patient made rapid improvement during the first month under treatment with gonadotropic substance from the urine of pregnant women. Should surgical intervention be considered, preoperative use of the extracts would perhaps lessen the operative risk. Whether surgical or medical treatment is indicated, the extracts should be employed in conjunction with whatever else is done.

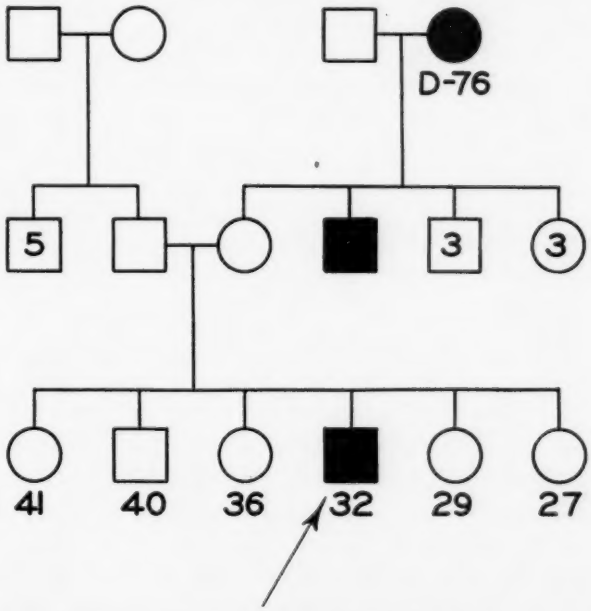
SUMMARY

A case of Simmonds' syndrome is reported in which glioblastoma multiforme was observed post mortem in structures adjacent to the pituitary gland and exerting pressure on the gland. It appears reasonable that the condition occurs frequently in a mild form but is mistaken for some similar condition. Certain aspects of treatment are discussed from both the medical and the surgical standpoint.

FAMILIAL OCCURRENCE OF TIC DOULOUREUX

WILLIAM ALLAN, M.D., CHARLOTTE, N. C.

Since the causes of tic douloureux are unknown,[1] any scraps of information tending to throw light on its source are worth collecting. I have recently encountered an instance of the familial occurrence of this malady, and last year Harris [2] published a pedigree in which 9 cases occurred in three generations. Harris has encountered 9 instances of the occurrence of trigeminal neuralgia in a child and one parent and



Genealogic chart. The squares indicate men; the circles, women; the numbers inside the figures, the number of sons or daughters; the numbers below the figures, the ages. The black figures indicate persons with neuralgia; the white, normal subjects.

2 of its occurrence in a child and one grandparent. The histories of these 12 families constituted 1 per cent of his series of cases. He found anticipation to be the rule, the age of onset in each succeeding generation being earlier than in the preceding one.

1. Horrax, G., and Poppen, J. L.: Trigeminal Neuralgia, Surg., Gynec. & Obst. **61**:394, 1935.

2. Harris, W.: Bilateral Trigeminal Tic: Its Association with Heredity and Disseminated Sclerosis, Ann. Surg. **103**:161, 1936.

REPORT OF A CASE

A white man aged 32 who was convalescing from resection of the sensory root of the right fifth nerve and who had suffered from tic douloureux for ten years was seen with the permission of Dr. J. W. Gibbon at the Presbyterian Hospital. A maternal uncle had undergone a similar operation some years before in Atlanta, Ga., but the trigeminal neuralgia eventually recurred on the other side. The maternal grandmother had suffered from similar attacks in the last years of her life: she would be sitting quietly, smoking a clay pipe, when the seizure would come and she would jump to her feet with a yell and grab her face, the pipe flying out of her mouth and the sparks showering down on any children who happened to be near.

CONCLUSION

The hereditary factor seems to be dominant rather than recessive, but, doubtless because of the importance of nonhereditary factors, the trait runs irregularly through the pedigrees.

It seems probable that a hereditary factor would be recognized in considerably more than 1 per cent of cases if it were sought.

Obituaries

FREDERICK PETERSON, M.D.
1859–1938

SOUND PSYCHIATRIST, GREAT SCHOLAR, TRUE POET

A FRIEND'S TRIBUTE

Of writing—obituaries—there is no end, especially if one has the sad experience of seeing many of one's closest friends pass to the Great Beyond. Obituaries, as such, I dislike writing, but a parting tribute soothes my own grief and helps to form a true estimate of the services rendered by the dead and of what this friendship, which had continued uninterruptedly for fully half a century, meant to him and to me.

In 1887, Peterson, of distinguished Swedish descent, born and educated in America, had finished his studies abroad and had served as assistant physician at the Poughkeepsie State Institution.

He came to New York, bringing a letter from a Harvard classmate of mine suggesting that we might find it mutually agreeable—young as we both were—to work together. We joined forces at the New York Polyclinic Hospital and began the research which resulted in the publication, in 1890, of "Infantile Cerebral Palsies," which, in its day, met with considerable favor. That any one has written dozens of articles means little. It was the spirit back of the work, the honest and unbiased search for truth, the enthusiastic support of genuine scientific inquiry, that made Peterson a most stimulating companion at a time when American neurology and psychiatry were beginning to achieve results that compelled general approval and some admiration.

To the names of Hughlings Jackson, Charcot, Erb and Westphal, the names of Weir Mitchell, the elder Hammond, Seguin and E. C. Spitzka were joined, properly enough, as those who were guiding the destinies of neurology and psychiatry; and a younger New York group [1] appeared on the horizon in the early eighties, including Starr, Dana, Peterson and, may I add, Sachs, to be joined a little later by Joseph Collins and Pearce Bailey.

In the next two decades, Peterson did excellent work as Starr's chief of clinic and later as professor of psychiatry at Columbia University, as head of the Craig Colony for epileptic patients, for the

1. There was a close bond with the Philadelphians—Mills, Spiller, Dercum and Burr.

development of which he was chiefly responsible, and as head of the New York State Commission in Lunacy. It was at this time, too, that he published his textbook in collaboration with Church and many—not too many—finely written articles in professional and lay journals on subjects within his own specialty and covering a wide array of cultural interests.

Above all else, Peterson was a great scholar, a lover of the arts and in his own right a distinguished poet. The poems of Pai Ta-Shun proved how thoroughly he had imbibed the spirit of Chinese art and Chinese life, and to his last days those who knew him well could think of him only as surrounded and influenced by his Chinese treasures. He seemed to be possessed of the judicial calm and insight of a Chinese philosopher.

In 1898 Dana, Collins, Peterson and I started the Charaka Club; during the next forty years, at the meetings of that club, Peterson was at his best when he recited "In the Shade of Ygdrasil" and other Chinese verses. It was at these meetings, too, that he gave his intimate associates the benefit of his unusual culture, his wide knowledge of the Orient and his deep insight into the spiritual and moral makeup of his fellowmen.

His abhorrence of sham, his unwillingness to be taken off his feet by fantastic doctrines of the day, made him a pillar of strength for those who, like him, were most anxious to direct the development of psychiatry in America along sound scientific lines. The greater the pity that he was not allowed to witness the further development of organic psychiatry now impending.

Peterson had a great sense of humor, which helped to develop a real joy of life. Only a few weeks before his death, I asked him how he felt. "Well, I have survived several incurable diseases; I have no right to complain." Many of us deplore the loss of a great physician, a true friend, a fine citizen.

As in "The Desert Garden" Pai Ta-Shun:

"I hear no more the swish of silk
  Along the marble walks;
The Autumn wind blows sharp and cold
  Among the flowerless stalks.

"In place of petals of the peach
  Fast drifts the yellow leaf;
And looking in the lotus-pond
  I see one face of grief."

BERNARD SACHS, M.D.

Abstracts from Current Literature

Anatomy and Embryology

THE MENINGEAL RELATIONS OF THE HYPOPHYSIS CEREBRI. HENRY G. SCHWARTZ, Anat. Rec. **67**:35 (Dec. 25) 1936.

An experimental and histologic study of the relations of the meninges to the hypophysis of the dog is presented. By means of cisternal injections of india ink, followed by fixation, decalcification and sectioning of the hypophysial region, the normal relations were preserved and clearly defined. The dura lines the sella turcica and fuses by delicate strands with the hypophysial capsule. The pia-arachnoid is reflected like a collar around the neck of the gland, so that the subarachnoid space invests only the stalk.

RIOCH, Boston.

NEUROFIBRILS IN LIVING GANGLION CELLS OF THE CHICK, CULTIVATED IN VITRO. PAUL WEISS and HSI WANG, Anat. Rec. **67**:105 (Dec. 25) 1936.

Spinal ganglion cells, explanted from chick embryos of from 8 to 11 days, were grown in tissue culture. Typical neurofibrils were observed to develop in the growing cells. These appeared as refractile, microscopic threads, which were concentrically arranged around the nucleus and extended in nearly straight parallel lines into the axons. The evidence is strongly in favor of the conclusion that neurofibrils exist as anatomic entities in living vertebrate nerve cells.

RIOCH, Boston.

THE MENINGEAL RELATIONS OF THE HYPOPHYSIS CEREBRI: I. THE RELATIONS IN ADULT MAMMALS. GEORGE B. WISLOCKI, Anat. Rec. **67**:273 (Feb. 25) 1937.

In a series of mammals, including a human fetus, the base of the brain and skull were sectioned serially after decalcification. It was demonstrated that the subarachnoid and subdural spaces surround the stalk of the pituitary gland, but terminate at the junction of the stalk and the body of the gland and do not extend into the sella. In the sella the capsule of the pituitary gland, the intrasellar dura and the adjacent periosteum form a continuous fused lamina.

RIOCH, Boston.

A STUDY OF THE VASCULARITY OF THE PITUITARY BODY IN THE CAT. HELEN M. STEVENS, Anat. Rec. **67**:377 (Feb. 25) 1937.

A gelatin mass to which carmine had been added was injected into the blood vessels of the hypophysis. Serial sections were cut, and the total lengths and average diameters of the capillaries in unit blocks of tissue from the four lobes were measured. The data are carefully analyzed, and the relative vascularity is given in terms of ratios of capillary volumes, surface areas, etc.; e. g., the capillary volume of the anterior lobe was 6, of the posterior lobe 1, of the pars intermedia 0.1 and of the pars tuberalis 5.

RIOCH, Boston.

DECREASE IN NUMBER OF MYELINATED FIBERS IN HUMAN SPINAL ROOTS WITH AGE. KENDALL B. CORBIN and ERNEST D. GARDNER, Anat. Rec. **68**:63 (April 25) 1937.

The myelinated fibers in the eighth and ninth thoracic dorsal and ventral roots were counted in 34 human cadavers, varying in age from 1 day to 89 years. The greatest number occurred during the second and third decades, with a gradual decrease, amounting to 32 per cent in the oldest subject.

RIOCH, Boston.

SOME STAGES IN THE DEVELOPMENT OF THE NEURAL COMPLEX IN ECTEINASCIDIA. ADOLPH ELWYN, Bull. Neurol. Inst. New York **6**:163, 1937.

In Ecteinascidia turbinata the hypophysial duct opens into the prebranchial portion of the pharynx before the formation of the mouth and at a considerable distance behind the latter. When the brachial aperture first appears the funnel is already lined with ciliated epithelium. Though it opens into the pharynx, the ciliated funnel when first formed is derived entirely from the neural tube and receives no contribution from the pharyngeal endoderm. Even the opening of the funnel is lined by hypophysial cells which have become incorporated in the roof of the pharynx. The adult ganglion is well developed in the late larval stages and is composed of a central fiber mass and a peripheral layer of nerve cells. The ganglion arises by cellular proliferation from the dorsal wall of the hypophysial duct posterior to the ciliated funnel and receives no contributions from the wall of the sensory vesicle.

KUBITSCHEK, St. Louis.

ON THE SIZE OF THE LARGEST NERVE CELLS IN THE FOURTH AND FIFTH LUMBAR GANGLIA OF THE ALBINO RAT, ACCORDING TO SEX. JOHN CHORNYAK, J. Comp. Neurol. **63**:489 (April) 1936.

Differences based on sex have been noted by other authors in the structural elements of the nervous system of the rat, notably in the peripheral spinal nerves, certain cranial nerves, the dorsal and ventral spinal nerve roots and the ventral horn cells, and in the relative total weight of the spinal cord. The present study concerns the differences based on sex in the size of the largest nerve cells in the dorsal lumbar ganglia of the albino rat. Direct comparison of the observed diameters showed that the cells were larger in the male than in the female, and that there was no significant difference between the diameters of the largest cells of the ganglia of the right and those of the left side. However, when cells were compared on the basis of body weight of the two sexes, the female showed the larger cells, both in diameter and in volume.

ADDISON, Philadelphia.

EVOLUTION OF THE MEDIAL GENICULATE BODY. JAMES W. PAPEZ, J. Comp. Neurol. **64**:41 (June) 1936.

By means of silver methods, Papez studied the medial geniculate body in brains of the turtle, alligator, lizard, snake and bat. The nucleus geniculatus medialis, pars ventralis, is the most caudal cell mass of the ventral thalamus. Its superficial position and its stability in the reptiles are taken as indications of its antiquity. The nucleus geniculatus medialis, pars dorsalis, is the most caudal of the dorsal thalamic nuclei. It develops from the posterior part of the nucleus reuniens, located behind and ventral to the medial thalamic nucleus.

Papez suggests that the dorsal part of the medial geniculate body originates as a lateral extension of the nucleus reuniens posterior and that its development is a gradual phylogenetic process which takes place as a neurobiotactic event along the course of the transversely directed fibers of the tractus tectoreuniens. In all forms the pars dorsalis is a dorsal thalamic structure, and the progress of its evolution is fully revealed in the various orders of reptiles. Its degree of development in the reptiles is in direct proportion to the size of the tractus reuniens and of the inferior colliculus.

FRASER, Philadelphia.

THE ACOUSTICO-LATERAL CENTERS AND THE CEREBELLUM, WITH FIBER CONNECTIONS, OF FISHES. ANTHONY A. PEARSON, J. Comp. Neurol. **65**:201 (Dec.) 1936.

This study was made to compare and homologize the acousticolateral centers and the cerebellum, with their fiber connections, in various species of cyclostomes, ganoids and teleosts. Complete series, cut in various planes and prepared for

study by the use of toluidine blue or pyridine-silver methods, were available. A progressive and correlated development of the acousticolateral area and the cerebellum was traced from cyclostomes through ganoids to teleosts. In cyclostomes the acousticolateral area presented only the beginning of the nuclear pattern characteristic of higher forms. In ganoids a ventral and a medial nucleus were differentiated. In teleosts a nucleus tangentialis and a nucleus vestibularis descendens were added. In cyclostomes the cerebellum represented a very primitive stage in phylogenic development. In the ganoids it presented a marked increase in size and differentiation as compared with that in cyclostomes. In teleosts it was still further advanced in size and differentiation. Thus, Pearson concludes that the nuclear configuration and fiber connections of the acousticolateral and cerebellar areas in cyclostomes, ganoids and teleosts afford an excellent illustration of progressive development and differentiation of these areas as they pass from primitive and more generalized to more specialized forms.

ADDISON, Philadelphia.

AN EXPERIMENTAL STUDY OF THE OPTIC TRACTS AND RETINAL PROJECTION OF THE VIRGINIA OPOSSUM. DAVID BODIAN, J. Comp. Neurol. **66**:113 (Feb.) 1937.

Bodian studied the projection of the retinal quadrants in the lateral geniculate body and the superior colliculus in 26 adult opossums. From eleven to thirteen days after operation the Marchi technic was applied. Brains were also studied in which the ocular bulb had been enucleated. In 1 opossum both ocular bulbs were removed, and eight weeks later the right striate area plus some parastriate cortex was removed. Six weeks after the last operation the animal was killed. The uncrossed retinal fibers were observed to occupy a lateral position in the chiasm and optic tract. Fibers from each retina ended in the dorsal nucleus of both lateral geniculate bodies, in both superior colliculi and in the contralateral nucleus opticus tegmenti. Sharp localization of fibers from the various retinal quadrants was seen in the superior colliculus and the lateral geniculate body. Projection of the retinal quadrants on the striate area was also delimited.

FRASER, Philadelphia.

A FURTHER INVESTIGATION OF AUDITORY CEREBRAL MECHANISMS. L. E. WILEY, J. Comp. Neurol. **66**:327 (April) 1937.

This study was undertaken to see whether destruction of the auditory area previous to the formation of an auditory habit interferes with the acquisition of that habit. Various parts of the cerebral cortex were removed from 13 rats. The animals were then trained according to a plan previously used with other animals. Wiley concludes that cortical destruction within the auditory cerebral mechanism does not interfere with formation of a simple auditory discrimination habit.

FRASER, Philadelphia.

PERIPHERAL AND CENTRAL CONNECTIONS OF THE UPPER CERVICAL DORSAL ROOT GANGLIA IN THE RHESUS MONKEY. KENDALL B. CORBIN, WILLIAM T. LHAMON and DONALD W. PETIT, J. Comp. Neurol. **66**:405 (April) 1937.

Because of the importance of the upper cervical dorsal roots in the cervical tonic and righting reflexes, this study was carried out to find the intramedullary terminations of fibers arising in the ganglia of the upper cervical dorsal roots in monkeys. The eleventh and twelfth nerves were also studied to determine the presence or absence of a sensory contribution from the second cervical dorsal root ganglion. In 5 monkeys the second and in 1 monkey the third cervical dorsal root ganglion was removed on the left. Most of the descending fibers from the second and third dorsal roots appear to terminate within one segment of their entrance into the cord. Few were seen three segments below the level of the

ganglion removed. Degenerating fibers were seen passing into the intermediate nucleus of Cajal, the ventral gray column, the homolateral dorsal column and the dorsal column of the opposite side. The accessory nerve was free from degeneration in all cases of removal of the second cervical dorsal root ganglion. In each case, however, the distal portion of the hypoglossal nerve on the side of operation contained degenerating fibers. The authors suggest that probably proprioceptive fibers to the hypoglossal nerve are contributed by the second cervical dorsal root ganglion.

ADDISON, Philadelphia.

THE FUNCTION OF THE BRAIN IN AUDITORY LOCALIZATION: II. THE EFFECT OF CORTICAL OPERATION UPON ORIGINAL LEARNING. L. A. PENNINGTON, J. Comp. Neurol. **66**:415 (April) 1937.

The purpose of this study was to consider the mechanism of the brain which underlies the response of the rat in a controlled situation requiring the animal to localize the direction from which a sound comes. Each of 48 male hooded rats was trained to run for food toward the source of a sound. The criterion of learning was selected at a 90 per cent level of accuracy for a period of three days. The animal was then subjected to a series of rigid experiments as a control. Each animal rested ten days and was then returned to the apparatus to be tested for retention. When the criterion of learning had been reached the second time, the animal was operated on and allowed to recover for ten days before being again studied for retention. The anatomic area was identified by retrograde degeneration in the medial geniculate body. No functional disturbance was noticed if the lesion was unilateral. The functional area of the cortex was delimited by an analysis of the behavioral data. The antomic and functional areas coincided within the limits of error. The greater the extent of bilaterality of the cortical lesion the greater the degree of amnesia.

FRASER, Philadelphia.

THE FUNCTION OF THE BRAIN IN AUDITORY LOCALIZATION: III. POSTOPERATIVE SOLUTION OF AN AUDITORY SPATIAL PROBLEM. L. A. PENNINGTON, J. Comp. Neurol. **67**:33 (June) 1937.

The results of the previous investigation were used as controls in this study of the postoperative behavior of the rat in learning to run for food toward the source of a sound. Operation in and about the region of the cortical auditory field was performed on 25 female rats. After a recovery period of ten days, the animals were retrained in localizing the noise. Pennington concludes that postoperative initial learning of an auditory spatial discrimination habit is not retarded and that either an all or nothing principle of neural function may exist within the auditory cortex or subcortical mechanisms may mediate the acquisition of the localizing response without retardation after cortical operation.

FRASER, Philadelphia.

A CORTICAL LESION CAUSING CELL REACTION IN THE ANTEROMEDIAL THALAMIC NUCLEUS. W. H. WALLER, J. Comp. Neurol. **66**:443 (April) 1937.

A lesion in the gyrus cinguli of a cat furnished evidence that the main cortical connection of the anteromedial nucleus of the thalamus in the cat is with the gyrus cinguli.

FRASER, Philadelphia.

CELLS AND FIBERS IN SPINAL NERVES: III. IS A 1:1 RATIO IN THE DORSAL ROOT THE RULE? J. F. BARNES and H. A. DAVENPORT, J. Comp. Neurol. **66**:459 (April) 1937.

Barnes and Davenport, of the Northwestern University Medical School, and Duncan and Keyser, of the University of Texas School of Medicine, counted cells and fibers in the same preparations of thoracic ganglia and their dorsal roots in

cats. The results showed wide differences in the counts made in the two laboratories. Cells of certain thoracic ganglia and fibers of their dorsal roots were then counted in a larger animal, the cow. Here, the fibers were larger, but a 1:1 ratio between the number of cells in a ganglion and the number of fibers in its dorsal root was not observed. Even when corrections were made for unmyelinated fibers which were not visualized in one section but could be seen in adjacent sections and for cut nucleoli, the majority of dorsal roots did not show the 1:1 ratio.

ADDISON, Philadelphia.

THE MECHANISM OF VISION: XIII. CEREBRAL FUNCTION IN DISCRIMINATION OF BRIGHTNESS WHEN DETAIL VISION IS CONTROLLED. K. S. LASHLEY, J. Comp. Neurol. **66**:471 (April) 1937.

Animals previously trained in reaction to light versus darkness in the Yerkes box lose the habit completely when the striate areas of the cortex are destroyed. Animals lacking the striate areas form the habit as rapidly as normal animals, but injury to the thalamus in addition to absence of the striate area retards or prevents formation of the habit. Experiments were planned to find whether loss of the brightness habit after destruction of the striate areas is due to abolition of the spatial properties of the stimulus. Two animals without lenses were successfully trained to choose the lighted and avoid the darkened alleys in a modified form of the Yerkes discrimination box. The striate area was destroyed by thermocautery, and the animals were retrained to the original criterion. Lashley concludes that 1 animal formed the differential reaction to light and darkness while completely lacking detail vision and lost the habit after removal of the striate area. The other animal confirmed these conclusions. Thus, it appeared that postoperative loss of the habit in animals with normal eyes is not due to interference with detail vision.

FRASER, Philadelphia.

DIAMETER OF THE AXIS CYLINDERS IN THE SPINAL NERVE ROOTS OF MAN. NILS ARNELL, Acta psychiat. et neurol. **12**:287, 1937.

Arnell measured the diameter of all axis-cylinders in all the spinal roots on the right side in a man aged 30. He used Agduhr's silver impregnation method. He confirmed the already known fact that there are more thin myelinated and nonmyelinated fibers in the dorsal than in the ventral roots. He divided the axis-cylinders of myelinated fibers according to their diameter into four groups: fibers of more than 3.7 microns, fibers between 3.7 and 1.48 microns, fibers between 1.48 and 0.74 microns and fibers of less than 0.74 microns. In a fifth group he included nonmyelinated fibers. The accurate counts of fibers in each group for all the ventral and dorsal nerve roots of the cord are shown in tables. Their numerical variations at different levels of the cord are represented by curves. It is shown that the myelin-free fibers in the dorsal roots of some segments (the third cervical, the seventh and eleventh thoracic and the fifth sacral) represent 50 per cent of the total fiber count; usually they represent from 30 to 40 per cent. Also, thin myelinated fibers represent a large part of fibers of the dorsal roots (up to 30 per cent in the sacral segments). In the ventral roots coarse fibers predominate, especially in the cervical and lumbar enlargements; in the seventh cervical and fourth lumbar segments they number as high as 60 per cent. In the eighth cervical and all the thoracic segments the ventral roots contain a considerable number of thin myelinated fibers (group 4). These probably are preganglionic sympathetic fibers. Nearly all the ventral roots contain nonmyelinated fibers, although their number is relatively small.

YAKOVLEV, Waltham, Mass.

Physiology and Biochemistry

THE EFFECT OF PYOCYANINE ON THE METABOLISM OF CEREBRAL CORTEX. LESLIE YOUNG, J. Biol. Chem. **120**:659, 1937.

It is known that certain dyes, among them pyocyanine, increase the oxygen consumption of living animal cells. In general, these dyes increase the oxygen consumption of tumors and of normal tissues having aerobic glycolysis, the effect being roughly proportional to the fermentative power of the tissues.

Young found that pyocyanine causes an initial increase in the oxygen consumption of slices of rabbit cerebral cortex but that this is followed by inhibition, which is irreversible and marked with high concentrations of the dye. The degree to which oxidation is accelerated in cerebral cortex by pyocyanine is dependent on the nature of the substrate added, the maximal effect being obtained with dextrose. No increased oxidation is obtained with pyocyanine in the absence of added substrate, and only a slight effect is observed with low tensions of oxygen.

Pyocyanine has a marked action on the glycolytic mechanisms of cerebral cortex. High concentrations of the dye cause increased aerobic glycolysis, the onset of which occurs during the period of respiratory stimulation. All concentrations of the dye tested increase anaerobic glycolysis initially, but the effect is maintained only with the lower concentrations. Pyocyanine has little effect on the respiration of cerebral cortex in the presence of a 0.001 molar solution of cyanide. With cerebral cortex treated with a 0.1 molar solution of potassium chloride, which is known to increase respiration and aerobic glycolysis, the initial increase in respiration under suitable conditions, due to the combined action of a 0.1 molar solution of potassium chloride and pyocyanine, is approximately equal to the sum of their separate effects.

PAGE, Indianapolis.

THE SPEED WITH WHICH VARIOUS PARTS OF THE BODY REACH EQUILIBRIUM IN THE STORAGE OF ETHYL ALCOHOL. R. N. HARGER, H. R. HULPIEU and E. B. LAMB, J. Biol. Chem. **120**:689, 1937.

It has been known since 1895 that alcohol when administered penetrates every tissue and fluid of the body. Harger, Hulpieu and Lamb made an intensive study of the rate at which various parts of the body attain storage equilibrium for alcohol. After oral administration to dogs of 3 Gm. of alcohol per kilogram of body weight, no changes were observed in the relation of the concentrations of alcohol in the blood, brain and liver during intervals of from fifteen minutes to twelve hours. The average ratios of concentrations of alcohol in 53 dogs (brain = 1) were: blood, 1.17 ± 0.09, and liver, 0.91 ± 0.07. With muscle there was a distinct lag during the first hour, but equilibrium was attained within three hours, after which the ratio for muscle and brain was 0.9 ± 0.03. After equilibrium resulted, alcohol was stored in about the same proportion as the water content of the materials analyzed. The average ratios on this basis (brain = 1) were: blood, 1.18 ± 0.08; liver, 0.94 ± 0.04; muscle, 1.01 ± 0.04; gastric contents, 1.13 ± 0.08; stomach tissue, 0.93 ± 0.06; upper part of the intestine, 0.97 ± 0.03, and lower part of the intestine, 0.99 ± 0.05. The ratios of the alcohol concentrations of the spinal fluid and those of the blood for 46 human subjects averaged 1.18 ± 0.09. On the basis of the average water content of these fluids, the recalculated ratio of the alcohol concentration of the spinal fluid and that of the blood was 0.996.

PAGE, Indianapolis.

THE METABOLISM OF PYRUVIC ACID IN VITAMIN B_1 DEFICIENCY AND IN INANITION. M. A. LIPSCHITZ, V. R. POTTER and C. A. ELVEHJEM, J. Biol. Chem. **123**:267, 1938.

The primary biochemical lesion associated with vitamin B_1 deficiency appears to be failure of the organism to metabolize pyruvic acid. Lipschitz, Potter and Elvehjem measured the oxygen uptake of homogenized tissue with and without

added pyruvate, as well as the removal of the pyruvate by the liver, kidneys and brain of normal, fasting and polyneuritic chicks. It was shown that the ability of the kidneys, liver and brain to utilize pyruvate as a substrate is impaired in animals with polyneuritis. The derangement is greatest in the brain. The liver and kidney of fasting birds show decreased ability to remove added pyruvate. The brain does not show this effect of fasting. Removal of pyruvates by the liver and kidney in fasting birds approximates that found in birds with polyneuritis. Oral administration of dextrose to fasting birds resulted in restoration of the ability of the liver to remove pyruvate. Similar feeding of dextrose to birds with polyneuritis resulted in deposition of liver glycogen and increased ability to remove pyruvate, though normal values were not reached. The failure in the case of polyneuritic birds to obtain complete restoration of the ability to remove pyruvate when dextrose was fed shows that inanition is not the sole explanation of the derangement of pyruvate metabolism, although it is a complicating factor.

PAGE, Indianapolis.

DOES THE DEVELOPING MEDULLA INFLUENCE CELLULAR PROLIFERATION WITHIN THE SPINAL CORD? S. R. DETWILER, J. Exper. Zoöl. **77**:109, 1937.

The medulla of Amblystoma was excised in embryos of stages 25 to 27 and replaced by a unit of spinal cord comprising the sixth, seventh and eighth segments. The embryos on which operation was performed were then fused parabiotically with a normal nurse, in order to maintain their nutrition; they developed as rapidly as did the nurse embryos. Histologic examination of the spinal cords of the two components showed that the cord of the experimental animal was often as completely developed as that of the normal animal. There was no consistent hypoplastic development of the cord in embryos lacking a medulla, providing the medulla had been replaced by another unit of nerve tissue. Since previous experiments have shown that hypoplastic development of the cord follows blocking of the medulla by insertion of a foreign structure and that hyperplastic development may be observed after intercalation of a supernumerary medulla between the normal medulla and the cord, the question arises concerning the supposed stimulative effect on cellular proliferation of projection fibers invading the cord from the medulla.

WYMAN, Boston.

AN OSCILLOGRAPHIC STUDY OF THE CEREBELLO-CEREBRAL RELATIONSHIPS. A. EARL WALKER, J. Neurophysiol. **1**:16 (Jan.) 1938.

The importance of interaction of the cerebrum and cerebellum has been stressed recently. Rossi showed that simultaneous stimulation of a lateral lobe of the cerebellum rendered a previously infraliminal stimulus capable of producing a motor response from the contralateral cerebral cortex. Walker made further studies of the cerebellocerebral relationship, using the isolated encephalon of the cat. This preparation was made by severing the medulla, with the cat under deep anesthesia. Artificial respiration was then used. Cortical potentials were led from the cerebral and the cerebellar cortex. Faradic stimulation of the cerebellar hemispheres produced changes in potential from the cortical motor areas and, to a lesser extent, from the parietal and temporal regions. These consisted of increased frequency and amplitude of the cortical waves. In only 3 of 21 experiments was cerebellar stimulation ineffective. The changes were greatly diminished by the application of procaine hydrochloride or ice to the cerebellar cortex. Asphyxiation, produced by the cessation of artificial respiration, prevented a response from the cerebral cortex to cerebellar stimulation. The application of strychnine to the cerebellar crotex failed in 2 instances to produce alterations in the cortical activity. Section of the cerebellar peduncle in 2 experiments abolished the response of the opposite motor cortex, but a slight change in the potentials of the ipsilateral motor cortex could still be elicited. Walker states that "the fact that the cerebellum is able to increase the activity of the motor areas leads to

the supposition that the former is exerting a stimulating influence on the cerebral cortex." The action appears to be one of sensitization of the cerebral cortex so that its threshold of stimulation is lowered.

ALPERS, Philadelphia.

FORCED CIRCLING MOVEMENTS IN MONKEYS FOLLOWING LESIONS OF THE FRONTAL LOBES. MARGARET A. KENNARD and LÉON ECTORS, J. Neurophysiol. **1**:45 (Jan.) 1938.

Primates from which the cortex of one cerebral hemisphere has been removed circle in walking toward the side of the lesion; such animals also show contralateral hemiparesis, together with deviation of the head and eyes toward the side of the lesion. With all types of progression there is rotatory movement which appears to be involuntary and purposeless and becomes accentuated under such emotional stimuli as rage, fear or the sight of food.

Kennard and Ectors attempt to analyze in the monkey the physiologic factors involved in circling and to localize the cortical area responsible for this symptom. They found that this syndrome is elicited in animals with frontal lobectomy. It was also found after unilateral and bilateral ablation of area 8. Deviation of the head and eyes toward the side of the lesion was produced by lesions of area 8. This became less marked during the first weeks after operation. Forced purposeless circling movements appeared coincident with deviation of the head and eyes. They also diminished in intensity, but persisted as hyperactivity for as long as a year. A "visual" defect was present contralateral to the lesion; it was not hemianopia but had to do with inability to respond to visual stimuli. The picture of "intellectual" deficit described by Bianchi following bilateral frontal lobectomy was attributed to the alterations in vision and motor performance described.

ALPERS, Philadelphia.

EXTRAPYRAMIDAL ACTION FROM THE CAT'S CEREBRAL CORTEX: MOTOR AND INHIBITORY. SARAH S. TOWER, Brain **59**:408, 1936.

This study deals with activity which is unequivocally extrapyramidal, activity which is obtained from the spinal cord after both pyramids are cut. Since in the cat no fibers have been described as passing from the cortex to the cord other than through the medullary pyramids, this distinction between pyramidal and extrapyramidal action is also that between direct corticosegmental action and action on the segmental mechanism through the intermediation of the brain stem. To investigate the extrapyramidal motor and inhibitory activity of the cerebral cortex, two lines of experimentation were followed: one, to determine the variety of such activities within the cortex and to outline their fields, and the other, to trace the projection downward from each field in a search for the subcortical mechanism on which the cortex acts. The experiments were performed on cats under ether anesthesia, except when decortication or decerebration rendered this unnecessary.

It was determined that widespread areas of the cat's cerebral cortex appear to be a source both of excitation and of inhibition throughout the length of the cerebrospinal axis. The motor function of the cortex is organized into two major parts. The corticospinal tract and the homologous tracts to the brain stem operate directly or through an internuncial neuron on the final common path to the effector organs; the extrapyramidal motor function operates indirectly, by facilitating the activity of lower mechanisms of the brain stem in which the form of the activity is determined. This distinction between pyramidal and extrapyramidal modes of operation is more apparent than real, for section of both corticospinal tracts in the cat diminishes initiative and slows initiation and performance but destroys no recognized element of the animal's activity, although the residual activity becomes stereotyped. Hence, the pyramidal tracts likewise appear merely to facilitate and to modulate the patterned activities of the lower motor mechanisms, but at the final segmental level rather than at the source.

The inhibitory function of the cerebral cortex is dominantly extrapyramidal. Reciprocal inhibition probably enters into corticospinal function as a property of the intrinsic mechanism of the cord on which this system must act, but no independent inhibitory action has been found in the system. The cortical inhibitory mechanisms probably act on the motor mechanisms of the brain stem engaged in producing movement or tone. Those effective against tonic contraction are localized and integrated with motor mechanisms, but are characterized by a lower threshold. The inhibition effective against movement is the most widespread activity demonstrable in the cortex, possibly representing a general cortical function.

The total organization of pyramidal and extrapyramidal action may perhaps be conceived as follows: The mechanism on which the cortex acts is organized into four levels; the segmental level is at the same time both the initial and the final site for integration. It projects to the periphery. The lower motor mechanism of the brain stem constitutes a level for reintegration and for production of the elements of posture and movement. It projects onto the segmental mechanism. The thalamic motor mechanism constitutes a level for further integration and for pattern formation and projects onto the lower mechanism of the brain stem, and not onto the segmental mechanism. The cerebellum is left out of consideration. The cerebral cortex represents the highest level of integration and projects onto each of the three lower levels. To the segmental level this projection is dominantly excitatory; to the higher levels excitation and inhibition are fairly equally matched. The cortical mechanism is able both to facilitate and to inhibit activity throughout the neural axis, either at the source or at the segmental level. This, however, is projected action. The prime function of the cortex itself must be so to integrate activity in these many projection systems that the final product of excitation and inhibition in the lower centers results in activity and cessation of activity in the effector mechanism, appropriate to the situation to be dealt with.

SALL, Philadelphia.

SYMPATHETIC GANGLIONIC RESPONSES IN MAN. B. BOLTON, D. J. WILLIAMS and E. A. CARMICHAEL, Brain **60**:39, 1937.

In recent years renewed attention has been paid to the possibility of synaptic connections between afferent and sympathetic efferent fibers within sympathetic ganglia. Schwartz, using the psychogalvanic reflex, demonstrated an alteration in the reflex when pressure was exerted on a limb which had been deafferented and had had all the white rami to its sympathetic ganglia cut. When all the gray rami were also cut no response occurred, but the cutaneous resistance due to this procedure had risen from 8,000 to 15,000 ohms. The results which Schwartz obtained do not necessarily indicate a ganglionic reflex and are explicable on a basis of altered circulation produced by the pressure on the limb, for Goadby and Goadby (1936) showed that the psychogalvanic reflex is dependent on the blood supply and is not necessarily evidence of a nerve reflex. Wernφe (1925), from his experiments on fishes, concluded that a sympathetic ganglion cell may have two neurons: one passing to the wall of the gut and the other to the integument, both being motor. After stimulation of the gut, alteration in distribution of pigment took place in the periphery. It is difficult to accept this hypothesis, as it means that a motor ending may also act as a sensory ending. On the other hand, Bain, Irving and McSwiney (1935), in a series of carefully controlled experiments on cats, showed that there is no synaptic connection between an afferent fiber from the gut and the cells within the sympathetic ganglia.

The present investigation was undertaken to determine whether there is a response dependent on an efferent fiber which passes directly to the sympathetic ganglion and there is in synaptic connection with the efferent cells. In 2 patients, plethysmographic records were taken from the digits of the hands and feet by a method previously described by Carmichael and Sturup. Vasomotor responses were elicited by various sensory stimuli while the subject was in a cold and in a

warm state. The authors concluded that in man no evidence was obtained to favor the presence of ganglionic vasomotor responses.

In the first subject, with the sympathetic ganglia and peripheral sensory neurons intact but with the cells in the lateral horn destroyed, it was impossible to produce any vasomotor responses in the legs. In the second subject, in whom it was possible to demonstrate that the sympathetic ganglia were functionally intact and that the afferent fibers were destroyed as they entered the cord, again no vasomotor responses were obtained by stimulation of the anesthetic zone. Thus, to produce in man a vasomotor response, it is necessary for the afferent fibers to reach the spinal cord and within the central nervous system to make connections either directly or by intercalated neurons with the cells of the lateral horn. It was not possible to produce a vasomotor response when sensory neurons and sympathetic ganglia were intact and the cord or the attachment of the sensory neurons to the cord was destroyed. This indicates that no ganglionic vasomotor responses can be obtained in man.

SALL, Philadelphia.

OPTOMOTOR REACTIONS OF CATS AFTER EXTIRPATION OF NEOCORTEX. O. GIRNDT and H. LEMPKE, Arch. f. d. ges. Physiol. **239**:544, 1937.

Three young cats were observed for five or six months after bilateral extirpation of the neocortex, particularly with regard to their ability to react to optic stimuli. After such extirpation the sense of smell first reappears, followed by hearing and finally by reactions to optic stimuli. The following optomotor reactions were elicited: (*a*) abnormal elevation of the forelegs and retardation of walking on change in brightness, e. g., if the animal walked into a dark room through a cone of light; (*b*) avoidance of obstacles, if they contrasted in brightness with the environment, and (*c*) movements toward moving objects that contrasted distinctly with the background. The view that decorticated animals show only "negative" manifestations of affects could not be confirmed. All 3 cats purred spontaneously on stroking and after the injection of small doses of morphine. In the 2 male animals symptoms of sexual activity were observed during the spring.

SPIEGEL, Philadelphia.

ACTION CURRENT OF MUSCLE ON DIRECT AND INDIRECT STIMULATION AND FUNCTION OF THE MOTOR END PLATE. H. GÖPFERT and H. SCHAEFER, Arch. f. d. ges. Physiol. **239**:597, 1937.

The action currents of the frog's sartorius muscle were studied with the cathode ray oscillograph while the blood supply of the muscle was preserved. On tetanic stimulation the nerve showed a frequency about twice that of the muscle (the ratio being 150:80 per second). The highest frequency for the sartorius muscle on indirect stimulation from the nerve usually was considerably lower than that on direct stimulation of the muscle. Thus, the end plate limits the frequency transmitted from nerve to muscle to a value which is lower than the highest frequency which the muscle is able to follow. This is interpreted as a protective function of the end plate against overstimulation of the muscle. Curarization does not change the form of the action current of the muscle on direct stimulation; only the rate of conduction is lowered. Before blocking the conduction from nerve to muscle, curare abolishes this function of the end plate, allowing higher frequencies of stimuli to pass than normally. After complete curarization one may lead off from the end plate a small, slow "end plate current," which lasts more than 25 milliseconds and measures a few tenths of a millivolt. The Wedensky inhibition is due to the fact that during continuous stimulation with high frequencies the end plate gradually ceases to transmit high frequencies to the muscle. There is antagonism between calcium ions and curare. Calcium protects against complete curarization by inhibiting the absorption by the muscle of curare from the blood.

SPIEGEL, Philadelphia.

SPONTANEOUS PRODUCTION OF ELECTRICAL POTENTIALS IN THE CEREBRAL CORTEX IN THE WAKING AND RESTING STATES. Z. DROHOCKI, Arch. f. d. ges. Physiol. **239**:658, 1937.

The electrical potentials originating in the exposed cerebral cortex of unanesthetized rabbits and rats were recorded by cathode ray and Matthews oscillographs. These spontaneous potentials showed great variability and a continuous change in the form of the curve, as well as fast quantitative changes, between 0.02 and 0.4 millivolt. This irregular course was interrupted by intervals in which some potential patterns repeatedly appeared, so that more or less definite cycles in potential production were formed. If the potentials of two cortical areas were recorded simultaneously, quantitative as well as qualitative differences in the curves were observed. In the main, the areas yielding such differences corresponded to distinct cytoarchitectonic areas; yet these local differences were so variable that one could not accept the theory that each cytoarchitectonic area produces a specific potential curve.

SPIEGEL, Philadelphia.

THE HUMAN ELECTROENCEPHELOGRAM. HANS BERGER, Arch. f. Psychiat. **106**: 165 (Jan.) 1937.

In the electroencephalograms of schizophrenic patients, Berger, unlike other authors, found no characteristic deviations from the normal, except when the patient was in an excited state or his attention was distracted by active hallucinatory experiences. In patients subjected to insulin treatment characteristic findings could be observed during the state of coma, consisting of bunching and a gallop rhythm of the alpha waves. Berger reiterates his belief in the existence of alpha and beta waves, both of which originate in the cortex. Electroencephalographic studies in monkeys by Dusser de Barenne indicated that the alpha waves come from the inner three layers of the cortex (IV, V and VI), and the beta waves from the outer layers (I, II and III). Berger believes that both these waves represent cortical activity and that the alpha waves, since they come from the inner layers, are more nearly related to the constant physiologic activities of the brain and the beta waves, coming from the outer layers, to psychic activities.

W. MALAMUD, Iowa City.

BIOELECTRIC ACTIVITY OF THE CEREBRAL CORTEX DURING NORMAL SLEEP AND DURING NARCOSIS INDUCED BY HYPNOTICS. R. KLAUE, J. f. Psychol. u. Neurol. **47**:510, 1937.

Klaue recorded bioelectric potentials from areas 3, 5, 7, 18, 19 and 21 of the cerebral cortex in cats during the waking state, normal sleep and sleep induced by chloral hydrate and barbital. Similar investigations were carried out with both these drugs on guinea pigs. The hypnotics were injected intraperitoneally.

Two principal phases were observed during normal sleep: sleeping phase I and sleeping phase II. The first sleeping phase was constant. Phase I was characterized by markedly irregular waves with a simultaneous increase in the potentials. Phase II follows phase I, but not constantly; in this phase the increased electrobiologic changes cease, and there ensues a period of repose. The millivolt production is diminished by one half. The second phase may return to the first phase at any time. All areas investigated yielded the same results during normal sleep. The form of the waves and the frequency of discharge, however, varied according to the anatomic structures of the area investigated.

The cortical hypnotic (chloral hydrate) as well the brain stem hypnotic (barbital) had characteristic effects on the cerebral cortex. Barbital produced periodic, repeated electrobiologic convulsive discharges. The latter did not occur in all the cortical areas. In the area striata, for instance, there was only an indication of convulsive spikes, and the discharges were unusually rapid. The appearance of convulsive currents depends on the dose of the hypnotic. With

chloral hydrate, even in lethal doses, convulsive currents did not appear. The potentials resembled those observed during inhalation of ether and chloroform. Here, too, the form of the curves depends on the structure of the respective areas.

Klaue refers to O. Vogt's researches on sleep and hypnosis. Vogt found that in man the beginning of spontaneous sleep is associated with loss of cutaneous sensibility and increase in muscle tonus, which during deep sleep is converted into atonia. This observation has also been confirmed by other investigators in animals. Vogt found similar manifestations in sleep induced by suggestion. Shortly before falling asleep muscle tonus is increased, and catalepsy of the limbs appears; as sleep becomes more profound the increased muscle tonus disappears and is replaced by hypotonicity. This transition is sudden. Vogt attributed these changes to partial "falling asleep" of the sensorimotor centers. It could be shown that these changes in muscle tonus occurred also in segments of the body in which anesthesia could be induced by suggestion. At the moment when the anesthesia was suggested there was an increase in muscle tonus, which sooner or later diminished and became lower than normal. The plethysmographic curves for muscle tonus during sleep induced by suggestion were identical with those obtained during anesthesia induced in a similar manner.

These findings are in accord with the electrobiologic manifestations from the areas of the cerebral cortex in cats during spontaneous sleep. Sleeping phase I, characterized by a considerable increase in potentials, corresponds to catalepsy of the limb, whereas sleeping phase II, characterized by potentials diminished below normal, corresponds to the atonic condition of the musculature.

KESCHNER, New York.

Neuropathology

OPTIC ENCEPHALOMYELITIS. J. ROSENBAUM, Arch. Ophth. **17**:694 (April) 1937.

Rosenbaum reports a case of optic encephalomyelitis in which autopsy was performed. The case was characterized clinically by rapid loss of vision in the left eye without recovery and by loss of vision in the right eye with partial recovery. Paralysis of the right leg and of the abdominal muscles followed about four months after onset of the disease in the optic nerves. Of special interest was the long interval between the occurrence of the ocular phenomena and the appearance of involvement of the spinal cord. Marked leukopenia was present during the entire course of the illness.

Microscopic examination showed fat in the optic tracts and demyelination of the optic chiasm. Many of the smaller vessels in this and other regions showed dilated perivascular spaces and cellular infiltrations. The spinal cord revealed patchy areas of demyelination and deposits of fat in various tracts at different levels. There was mild cellular infiltration of the meninges.

SPAETH, Philadelphia.

TERATOMA OF THE PINEAL BODY. S. JUDD BOCHNER and JOHN EDWIN SCARFF, Arch. Surg. **36**:303 (Feb.) 1938.

Bochner and Scarff advocate the theory that the impulse for embryonal tumor formation within the pineal body originates in an inherent multipotentiality in the primitive cells of the pineal body similar to that in cells of the testis and ovary. They report a new case of teratoma of the pineal body in which a unique feature was the presence of teeth in all stages of development, up to the adult form. Such formations have not been reported in a case of teratoma of the pineal body prior to this time. Similarly unique formations were seen in the extensive development of structures identified with the nasopharynx and with the thyroid gland.

GRANT, Philadelphia.

PATHOLOGIC AND HEREDITARY FEATURES OF WILSON'S PSEUDOSCLEROSIS. W. MÜLLER, Deutsche Ztschr. f. Nervenh. **145**:234, 1938.

Müller reports a case of Wilson's disease in which the patient died after about nine months. The clinical manifestations were typical and included athetosis, grimacing, rigor and the Kayser-Fleischer rings. Of particular interest were striae on both thighs. There were also abnormal height, small testes and other indications of possible endocrine disturbance. There were evidences of a tendency to purpura. At autopsy, characteristic changes in the lenticular nucleus were observed. Histologically, the lesions showed the Alzheimer type of gliosis, but no cyst formation. The liver was cirrhotic, and the spleen showed changes resembling those seen in Banti's disease. One sister had symptoms extremely suggestive of Wilson's disease; the father had pernicious anemia with degeneration of the spinal cord.

PUTNAM, Boston.

ACUTE MULTIPLE SCLEROSIS WITH CYST FORMATION. A. JUBA, Deutsche Ztschr. f. Nervenh. **145**:275, 1938.

A man aged 36 died nine months after the onset of an illness characterized by ataxia of the hands and later by paraplegia. Bronchopneumonia caused death. At autopsy typical plaques of demyelination, with relative preservation of axis-cylinders and gliosis, were seen scattered throughout the brain and spinal cord. Many vessels were thickly infiltrated with cells. Mild changes were seen in the gray matter where this was encroached on by the process. There was a tendency to the formation of "maplike" areas. In the center of a typical plaque in the left hemisphere an area of cystic softening was observed. Immediately about it were unusually extensive destruction of axis-cylinders and glia cells and marked proliferation of vessels.

PUTNAM, Boston.

CEREBRAL CHANGES IN AN ACUTE CASE OF FAT-EMBOLISM. J. CAMMERMEYER, Acta psychiat. et neurol. **12**:333, 1937.

Cammermeyer reports the case of a man aged 29 with acute mental disturbances, hallucination and flexion contracture of the lower extremities. After orthopedic correction of the contractures, with the patient under light ether anesthesia, he became comatose and died about twenty-nine hours after the operation. Post-mortem study revealed multiple foci of fat embolism throughout the brain. Within the foci acute changes in the nerve cells and regressive glial reactions were seen. The absence of progressive glial reactions led the author to regard the process in the embolic foci as "coagulation necrosis." The diffusion of the lesions, as well as the shape and size of the foci, appeared to depend solely on the ischemic effect of emboli. In the regions of similar cellular, myelinic and angioarchitectonic structure, the foci of postembolic necrosis were of similar shape and size. Variations in the size of the foci were assumed to be due to the local variations in the density and type of capillary network.

YAKOVLEV, Waltham, Mass.

Vegetative and Endocrine Systems

PRECOCIOUS PUBERTY FOLLOWING ENCEPHALITIS. F. R. FORD and H. GUILD, Bull. Johns Hopkins Hosp. **60**:192, 1937.

Two young girls showed precocious sexual development after measles encephalitis, and a boy, premature development of the sex organs as well as sexual misbehavior after epidemic encephalitis. A survey of the literature indicates that destructive lesions in the region of the pineal body and in the walls of the third ventricle may result directly or indirectly in the syndrome of macrogenitosomia

praecox. Cases are cited in which this syndrome was associated not only with a tumor arising in the region of the pineal body but with a tumor of the hypothalamus. The same syndrome is known to follow inflammatory processes, such as meningitis, meningoencephalitis and epidemic encephalitis. The information available indicates that the pineal body does not play a significant role in the production of macrogenitosomia praecox, for the gland is normal in many cases in which this syndrome is fully developed and destruction of the pineal body may be followed by no apparent change in the genital organs. The authors have failed to find a single instance in which definite macrogenitosomia praecox was associated with a verified pinealoma. FROM THE AUTHORS' SUMMARY. [ARCH. PATH.]

THE EFFECT OF SPLENECTOMY ON THE WEIGHT OF THE HYPOPHYSIS OF THE ALBINO RAT. L. F. EDWARDS and C. W. WRIGHT, Endocrinology **21**:808 (Nov.) 1937.

Edwards and Wright removed the spleens of 50 female albino rats. Fifty additional female albino rats of various ages served as controls. The animals were killed two weeks after splenectomy, and the hypophyses were removed and examined. The difference in weight between the hypophyses of the splenectomized animals and those of the animals used as controls was significant and was not due to random sampling. The difference in body weight of the two groups of animals was not significant. The difference in the relation of the weight of the hypophysis to that of the body, expressed in percentages, was significant. The resulting hypertrophy of the hypophysis raised the question whether this effect was indicative of an endocrine function on the part of the spleen or whether it was attributable to a compensatory reaction of the reticuloendothelial element of the hypophysis, resulting from loss of the spleen. Preliminary histologic examination of the hypophyses removed from some of the animals subjected to splenectomy showed increased vascularity, increase in the reticuloendothelial cells and hyperplasia of the basophilic cells, as evidenced by a marked increase in mitotic activity.

PALMER, Philadelphia.

THE CUSHING SYNDROME. C. W. DUNN, Endocrinology **22**:374 (March) 1938.

Dunn reports the results of treatment of 11 patients, all women, with a disease clinically diagnosed as the Cushing syndrome. Six patients, who received large doses of estradiol benzoate (progynon B) or of estradiol (progynon D H), alone or combined with progesterone, over a period of from three to twelve months, showed excellent or very good results. Two others treated over periods varying from one to four years showed consistently good results during the period of intensive therapy. In 1 patient who received low doses of estradiol for eighteen months there developed gradually the characteristic features of the Cushing syndrome, but subsequent intensive therapy with estradiol benzoate promptly relieved the symptoms. Two other patients were relatively untreated, and both died of pneumonia. Estradiol benzoate therapy can be maintained for long periods without untoward effect and is regarded as inhibiting anterior pituitary function and basophilic changes. The author's cases may be considered to represent the benign form of the Cushing syndrome.

PALMER, Philadelphia.

CHROMOPHOBE ADENOMA OF THE PITUITARY ASSOCIATED WITH CUSHING'S SYNDROME. C. J. FULLER, Lancet **2**:181 (July 25) 1937.

In 1934 Fuller reported a case in which were noted the clinical features of basophilic adenoma of the pituitary gland. One year later autopsy revealed a chromophobic adenoma of the gland. The patient, a man aged 20, presented the following features typical of Cushing's syndrome: plethoric complexion; increase in the subcutaneous fat of the face, neck and trunk; well developed striae; increase

in blood pressure; loss of libido, and decrease in sugar tolerance. High voltage roentgen therapy failed to arrest the progress of the condition. Autopsy showed that the anterior lobe of the gland was occupied by an adenoma measuring 1.3 by 0.85 cm. On examination Dorothy Russell found the adenoma to be chromophobic in type. The granules of the acidophilic cells stained brightly with acid fuchsin, anilin blue and Mann's eosin-methylene blue (methylthionine chloride) stains. The cytoplasm of the basophilic cells showed a conspicuous degree of hyaline change. Fuller calls attention to the fact that the syndrome has been described in patients with tumor or hyperplasia of the adrenal cortex. It has also been noted in 2 cases of carcinoma of the thymus and in another case of chromophobic adenoma of the pituitary gland.

WATTS, Washington, D. C.

EXISTENCE OF A HEMATOPOIETIC HORMONE IN THE HYPOPHYSIS. J. FLAKS, I. HIMMEL and A. ZLOTNIK, Presse méd. **45**:1261 (Sept. 4) 1937.

Flaks and his collaborators maintain that the hematopoietic function of the bone marrow is regulated by a hormone, although its character and origin have not been definitely established. Clinical and experimental observations indicate that the hypophysis exerts an influence on the hematopoietic function of the bone marrow, and the authors decided to investigate that problem also. They experimented on rats by injecting extracts of the anterior lobe of the hypophysis. In summarizing the experiments they state: 1. The prolonged oral administration of the anterior lobe of the hypophysis produces in rats an increase in the number of reticulocytes and consecutive augmentation in the erythrocytes, so that the number of erythrocytes which is normal for this species of animals is considerably surpassed. There results prolonged experimental polyglobulism. 2. The substance which irritates the bone marrow and provokes strong erythrocytosis is not found in the deproteinized fraction and is thermostable. 3. This hormone acts directly on the bone marrow and is without influence on the thyroid. 4. The injection of a quantity of extract corresponding to 0.4 Gm. of fresh hypophysis produces after twenty-four hours transformation of gray into red marrow. 5. On the basis of clinical observation and the experiences described, the authors conclude that the hypophysis has an important physiologic role in the regulation of erythropoiesis by means of a hematopoietic hormone which acts on the bone marrow.

EDITOR'S ABSTRACT.

THE HORMONAL FACTORS IN EMOTION. G. MARAÑON, Rev. franç. d'endocrinol. **15**:443 (Dec.) 1937.

Marañon theorizes on the role played by hormones in the production of the emotions. He claims that the facts available allow the formulation of an organic mechanism of emotion. He traces the pathway of this mechanism from the cortex to the autonomic centers of the diencephalon and to the peripheral endocrine apparatus, where the "visceral commotion" takes place. This visceral manifestation, he believes, is an essential phenomenon for the conscious appreciation of emotional states. He advises observation of emotions on one's own person, an approach which he thinks is better than that used by the "intellectualist" or the "physiologist." This self observation, according to Marañon, teaches not only that emotion is a peripheral phenomenon but that without the "visceral commotion" which is perceived by consciousness there would be no emotion. This approach, he also claims, shows that emotion may be produced in a reversible manner; that is, it may originate in the peripheral visceral manifestations. In certain cases, Marañon believes, this reversible mechanism may become habitual, as it manifests itself in certain pathologic states, such as thyroid conditions, and even normally in persons of certain professional types, such as artists.

NOTKIN, Poughkeepsie, N. Y.

Treatment, Neurosurgery

VACCINATION AGAINST EXPERIMENTAL MENINGOCOCCIC MENINGITIS. J. KOLMER and A. M. RULE, Am. J. Clin. Path. **8**:1 (Jan.) 1938.

Kolmer and Rule immunized guinea pigs, rabbits and monkeys by the subcutaneous injection of from three to five weekly doses of types I and III meningococcus vaccines cultivated in hormone broth for five days and sterilized with cresol. All showed the production of varying amounts of agglutinin. The serums of immunized monkeys also showed the presence of complement fixing antibody. Four weeks after the last doses of the vaccine the guinea pigs and rabbits were tested for acquired resistance by the intracisternal inoculation of living virulent meningococci. The monkeys were tested by the intraspinal inoculation of the organisms. All of 12 unvaccinated guinea pigs used as controls died of severe meningitis in from twenty-four to seventy-two hours. Of 28 vaccinated animals, 5 recovered. Of 12 unvaccinated rabbits used as controls, 10 died. Of 28 immunized animals, 15 died and 13 recovered. All of 6 unvaccinated monkeys used as controls showed moderately severe symptoms of meningitis, but recovered. Of 13 immunized animals, 3 probably showed symptoms of meningitis with recovery while the remaining 10 remained well. These results are believed to lend encouragement to efforts for the vaccination of human beings against meningococcic meningitis.

EDITOR'S ABSTRACT.

RELIEF OF NEURITIC PAIN BY ARTIFICIAL FEVER THERAPY. A. E. BENNETT and P. T. CASH, Arch. Phys. Therapy **19**:69 (Feb.) 1938.

Bennett and Cash have used the hypertherm for the induction of artificial fever in a large variety of diseases. Up to Jan. 1, 1937, in twenty-six months, they treated 581 patients, who received more than 2,650 fever treatments. Of these patients, 40 underwent fever therapy in an attempt to obtain relief from severe neuritis, myalgia or a radicular painful state. There were 20 patients with sciatic neuritis, 6 with brachial neuritis, 5 with toxic-infectious polyneuritis and infective neuronitis, 3 with herpes zoster, 2 with lymphocytic meningitis and 4 with miscellaneous arthritic states with secondary neuritis or neuralgia. All types of neuritic pain were relieved immediately, but pain recurred in some cases, especially in those of secondary neuritides resulting from compressive lesions. This form of heat therapy (with temperatures from 103 to 105 F.) is a distinct advance over all forms of local use of heat in relieving pain. Fever therapy is recommended not as a substitute for other accepted forms of therapy for neuritis but only as an aid in the management. It probably hastens convalescence in the severe toxic-infectious polyneuritic states. The physiologic mechanism by which general fever induction effects relief from neuritic pain is not well understood. Undoubtedly, the enhanced blood flow and peripheral vasodilatation in the inflamed areas increase tissue oxidation and nutrition. Leukocytosis, phagocytosis and mobilization of immune bodies secondary to induction of fever play a part in the absorption of deposits occurring in rheumatism, dilution of toxins and the healing of inflamed nerve tissues. The treatments do not interfere with any other indicated therapy and are practically without danger in experienced hands.

EDITOR'S ABSTRACT.

TREATMENT OF EPILEPSY IN CHILDREN. H. M. KEITH, Canad. M. A. J. **37**:485 (Nov.) 1937.

A ketogenic diet, producing large amounts of diacetic acid in the urine, is a satisfactory method of treating epilepsy, particularly in children. Keith has treated 160 patients satisfactorily over a period of from one to nine years. Of these, 36 per cent remained entirely free from attacks of any type so far as is known to themselves or to their parents; 21 per cent were improved, having only an occasional attack; 43 per cent were not benefited, although they carried out instructions fully.

Therefore with the ketogenic diet alone one third of epileptic children can be made free from seizures, and from 50 to 60 per cent can be improved. A ketogenic diet, to be effective, must be rigidly controlled and should be weighed. It is necessary that in the diet the ratio of the ketogenic to the antiketogenic material be at least 3:1. For children the number of calories is 55 per kilogram, or 25 per pound, of body weight. The amount of protein is set at 1 Gm. per kilogram of body weight. The carbohydrate and the fat are then adjusted so that the ratio is as indicated and the calories are satisfactory for nutrition and growth. In using diet or medication, one must not lose sight of the necessity for healthy outdoor exercise, adequate rest and general hygienic measures. EDITOR'S ABSTRACT.

REMISSIONS OF ATTACKS IN EPILEPSY TREATED WITH SODIUM BROMIDE. L. J. POLLOCK, J. A. M. A. **110**:632 (Feb. 26) 1938.

In order to determine the number of patients whose epileptic attacks were completely stopped for the duration of treatment with sodium bromide and the duration and character of remissions brought about when attacks occurred at times during the period of treatment, Pollock selected all private patients suffering for a period of more than four months from a convulsive disorder who reported to him at regular intervals from January 1936 to January 1937. There were 96 such patients. Of these, 85 had been treated for more than a year, and some had been observed for many years. Of the 96 patients, 10 suffered from petit mal attacks alone, 27 from grand mal attacks alone and 41 from both types. In 28 of the 96 patients all attacks were stopped from the beginning of treatment. Final remissions beginning with the institution of treatment or shortly after occurred in 35 patients, or 36 per cent. In 35 other patients remission of attacks occurred; attacks then returned and again disappeared. Of the entire group, remissions were reported at the last visit by 70 patients (72.9 per cent)—of less than a year, by 31; of from one to two years, by 12; of from two to three years, by 11; of from three to four years, by 4; of from four to five years, by 3; of from five to six years, by 1; of from seven to eight years, by 3, and over eight years, by 5. Eleven of the 39 patients with a final remission of less than a year were treated less than a year. Of the 85 patients treated more than a year, final remissions occurred in 63, or 74 per cent, and have lasted more than a year in 39, or 45.8 per cent. In many instances, when the final remission was of less than a year remissions of much longer duration had occurred before. Of a group of 22 patients with a final remission of less than five months, 18 had had remissions of over one year. Of 85 patients treated longer than a year, remissions of more than a year were brought about in 61, or 71.7 per cent. Of the total of 96 patients, remissions were brought about in 78, or 83.4 per cent. For 18 patients (18.7 per cent) the treatment was completely ineffectual. When remissions are brought about by treatment, it must be continued throughout the life of the patient. It is suggested that early treatment and few previous attacks lead to more prompt and continued remissions.

EDITOR'S ABSTRACT.

CHEMOPROPHYLAXIS IN POLIOMYELITIS: TECHNIC OF APPLYING CHEMICAL AGENTS TO THE OLFACTORY MUCOSA. L. SHAHINIAN, J. A. BACHER, R. C. MCNAUGHT and R. R. NEWELL, J. A. M. A. **110**:1254 (April 16) 1938.

The evidence that a chemical agent such as 1 per cent zinc sulfate confers on monkeys a high degree of resistance against poliomyelitis virus for at least one month after treatment suggests that such a prophylactic measure may deserve a trial in human beings during periods when poliomyelitis is prevalent. Shahinian, Bacher, McNaught and Newell concern themselves primarily with devising a method of applying the prophylactic treatments that can be easily and accurately used by the physician with a minimum of discomfort and risk of injury to the patient. They have roentgen and clinical evidence that when the head is completely inverted, with the base line horizontal, limited quantities of fluid introduced

slowly into the olfactory sulcus at the limen nasi will flow along the groove and accurately fill the inverted common nasal meatus, in a selective manner, to a height usually sufficient to immerse most of the estimated olfactory area. Previous shrinkage of the nose was found necessary. All solutions placed in the nose were found to be better tolerated when previously warmed to body temperature in a water bath. Ordinary medicine droppers, previously calibrated for volume, are used. With a speculum spreading the anterior naris, the tip of the dropper is inserted approximately 0.5 cm. into the naris, at the anterior angle of the nose, without touching the sensitive mucous membrane of the walls. The fluid is introduced slowly and steadily, drop by drop. The patient is kept in the inverted position one minute after the last drop has entered. At the end of treatment, the solution may be emptied by the route of entry by having the patient turn over into the prone position, lift his head and sniff outward. This procedure prevents unpleasant effects on the throat due to the patient's swallowing the solution. The approximate quantity of fluid necessary to immerse adequately the olfactory membrane by this method is 0.5 cc. for children less than 10 years; 0.4 cc. for children between 10 and 14 and 0.25 cc. for adults are probably sufficient; a portion of the fluid will overflow in some instances.

EDITOR'S ABSTRACT.

DRAINAGE OF CEREBROSPINAL FLUID IN TREATMENT OF HYDROCEPHALUS, SYRINGOMYELIA AND SYRINGOBULBIA. N. D. ROYLE, J. A. M. A. **110**:1264 (April 16) 1938.

Shrinkage of the brain on the side on which the stellate ganglion was removed suggested to Royle that the operation of superior thoracic ganglionectomy might be used in the treatment of hydrocephalus. He treated 2 patients in this manner. The operation of superior thoracic ganglionectomy causes an increase in the rate of capillary flow in the cervical region of the spinal cord and in the brain. The operation of lumbar sympathectomy increases the rate of drainage on the ipsilateral side of the cord in the lumbar region. Both operations provide an outlet for the cerebrospinal fluid where they tap the spinal circulation. In contrast to the other methods of draining the cord, this method has the virtue of permanence. Epinephrine has little effect after sympathetic denervation.

EDITOR'S ABSTRACT.

SYMPTOMATIC TREATMENT OF PARKINSONIAN SYNDROME WITH COBRA VENOM. R. F. GAYLE JR. and J. N. WILLIAMS, South. M. J. **31**:188 (Feb.) 1938.

It is generally accepted that cobra venom is a neurotoxin which acts on the higher nerve centers of the brain. The use of a solution of cobra venom in the treatment of the parkinsonian syndrome suggested itself to Gayle and Williams because it has been proved that intramuscular injections may relieve chronic pain; in view of the fact that certain patients having paralysis agitans suffer from pain, it was decided to use this product in the hope of relieving parkinsonism. It was found in certain cases of the parkinsonian syndrome that not only was the pain relieved but certain other symptoms, such as increased spasticity and tremor, were benefited. Cobra venom was used for 18 patients with well developed signs and symptoms of the parkinsonian syndrome. They exhibited the typical signs of muscular rigidity, nonintention tremors, masked facies, pains and altered gait. The ages of the patients varied from 21 to 69 years. The method of treatment followed in each case was intramuscular injection of 0.5 cc. of cobra venom the first day and 1 cc. every other day for ten doses. If no subjective improvement was effected by this number of doses, the treatment was discontinued. In all who showed improvement, the interval between doses was lengthened, with no increase in symptoms. The most striking effect of the cobra venom was the relief from pain. Usually the pains were relieved after about the fourth or fifth injection, and this has lasted until the present. In 67 per cent of the cases there was marked subjective improvement, but little objective change was noted. These patients stated

that there seemed to be less muscular rigidity and that they were able to perform tasks which were impossible before treatment. Improvement was noted in that they were encouraged, more cheerful and decidedly less nervous. Thirty-three per cent of the patients who showed no improvement were older than the average, and the duration of the disease was much longer. Cobra venom solution is a valuable aid in the symptomatic treatment of the parkinsonian syndrome; it has a cumulative effect when given intramuscularly in small doses, and it can be partially substituted for drug therapy in certain forms of the disease.

EDITOR'S ABSTRACT.

STREPTOCOCCAL MENINGITIS: SULPHANILAMIDE IN ITS MANAGEMENT. TERENCE CAWTHORNE, Lancet **1**:304 (Feb. 5) 1938.

The mortality from meningitis of streptococcic origin has markedly diminished since the advent of sulfanilamide in the treatment of this disease. Streptococcic meningitis constitutes about 6 per cent of all the meningitides, and about one third of all forms if those due to the meningococcus and tubercle bacillus are eliminated. The streptococci gain entry from otitic and respiratory infections and from the nose and as a result of trauma to the head. Sulfanilamide is the treatment of choice. Large doses are advised, the maximum dose being 1 Gm. per 20 pounds (9.1 Kg.) of body weight in twenty-four hours. Oral administration in divided doses every six hours is preferable, but a 0.8 per cent solution may be given subcutaneously to delirious patients and to children every twelve hours. The author believes that the primary focus should be left alone when the meninges have been infected by the vascular route and that immune mechanisms should be allowed to function. Conditions of traumatic origin should be handled conservatively, whereas primary foci of osseous involvement should be removed as early as possible.

KRINSKY, Boston.

SCIATICA AND ITS TREATMENT WITH REFERENCE TO EPIDURAL INJECTION. G. SLOT, M. Press **196**:15 (Jan. 5) 1938.

The method used by Slot in the treatment of sciatica was a combination of epidural injection and manipulation, with the patient under anesthesia induced with evipal (sodium *n*-methylcyclohexenylmethylmalonylurea). The advantages claimed for this method are the rapidity of treatment, the simplicity of the technic and the high percentage of cures obtained as compared with other methods. The two principles of the treatment are: the stretching of the nerve roots by the harmless fluid and the manipulation. The needle must first be introduced in the sacrococcygeal foramen at an angle of about 70 degrees to the skin; to enter the canal, the direction must be changed to an angle of about 20 degrees to the sagittal plane. One can feel when the needle is in the right place; from 50 to 100 cc. of warm 1 per cent procaine hydrochloride in sterile physiologic solution of sodium chloride is injected slowly, the dose varying with the size of the patient. As the fluid enters, the resistance is found to increase; the needle is then withdrawn, and the puncture is sealed with adhesive plaster. Manipulation is now performed. This consists first in hyperextension of the lumbar portion of the spine; the knee is placed in the hollow of the back, and both legs are firmly and gently pulled against it. The patient is then turned around; the knees are straightened, and both legs, one after the other, are forced on the pelvis (the pelvis being fixed by an assistant), so as to stretch the sciatic nerve. On recovery, some analgesic is prescribed for pain, and massage is given the next day. In the majority of the author's cases this treatment was all that was necessary; in 20 per cent, however, a second injection was required. In the majority of the series of more than 200 cases the condition had been intractable and had resisted the usual methods of treatment. In cases of osteoarthritis of the hip the manipulation was reduced to a minimum, although slight manipulation acting with the epidural injection was most helpful to the patient. This does not apply in cases in which there is bony ankylosis. While

no cure can be promised, patients have been pleased with the great alleviation of pain that has resulted, and the treatment can, if necessary, be repeated in six months.

EDITOR'S ABSTRACT.

ASEPTIC MENINGITIS ASSOCIATED WITH AUTOHEMOTHERAPY AND AUTOCEREBROSPINAL FLUID TREATMENT OF MULTIPLE SCLEROSIS. G. TÀNFANI, Minerva med. **1**:225 (March 3) 1938.

In 40 cases of multiple sclerosis Tànfani resorted to Boschi's treatment, which consists in the production of aseptic meningitis followed by intramuscular injections of the patient's own blood and cerebrospinal fluid. Aseptic meningitis is produced by injecting from 2 to 5 cc. of double distilled water into the spinal canal. The patient's own blood, in small progressive amounts not specified by the author, is injected six or seven hours later. The amount of cerebrospinal fluid in each injection is 5 cc. The total number of treatments varies from two to four. Intervals of two or three weeks are allowed to pass between the treatments. In the author's cases the condition was grave and of long duration. Recovery (except for the organic defects) took place in 3 cases; great improvement in 6 cases, and moderate improvement in 13 cases. The treatment failed in 18 cases. The reaction consists of headache, vomiting, pain in the extremities and vertebral column, flexor spasms, elevation in temperature to between 39 and 40 C. (102.2 and 104 F.) and intense lymphocytosis of the cerebrospinal fluid. The benefits of the treatment are evident after the second or third injection in the majority of cases. The best results from the treatment are attained in patients who show an intense meningeal reaction and no tendency to spontaneous reactions, especially if the disease is of the cerebellopyramidal type and has lasted for less than six years. The satisfactory results of the treatment cannot be mistaken for spontaneous reactions.

EDITOR'S ABSTRACT.

ATTEMPT AT NEW THERAPY OF NARCOLEPSY. L. FESSLER, Wien. med. Wchnschr. **88**:125 (Jan. 29) 1938.

Fessler points out that for symptomatic narcolepsy that is not caused by tumors, syphilis or trauma there is as yet no satisfactory treatment. Nitschke's observation that hibernation of hedgehogs could be prevented by the administration of irradiated ergosterol induced Fessler to try it for patients with narcolepsy. He reports the histories of 2 cases in which he resorted to this medication. In the first case no treatment of any kind was given during the first eight days, and there was no change in the narcolepsy. Thus, the objection is answered that change in surroundings alone will produce considerable improvement in narcolepsy. After the eighth day the patient was given 10 drops twice daily. During the first two days of this medication there was no change, but during the subsequent nine days the patient was entirely free from attacks, although there still were times when he felt tired. On each of the twelfth, sixteenth and twenty-third days after the beginning of the treatment, one attack occurred. After the patient's return to the home surroundings, the attacks of narcolepsy recurred when no irradiated ergosterol was taken, but they became much less frequent when it was taken again. For a more objective estimation of the effect of irradiated ergosterol, complete abstinence from alcohol was enforced for weeks. It was found that this reduced the incidence of the attacks of narcolepsy, but only when irradiated ergosterol was given at the same time did the attacks stop completely. In order to avoid an excessive dose and its possible dangers, the calcium content of the serum was kept under constant supervision: It remained approximately normal. In the second case the medication with irradiated ergosterol was not quite as effective as in the first. The second patient was much older than the first, and the treatment was begun with smaller doses. When complete abstinence from alcohol was enforced and comparatively large doses of irradiated ergosterol were given, the attacks of narcolepsy ceased.

EDITOR'S ABSTRACT.

Muscular System

APPARENT MYOPATHIC AMYOTROPHY IN TWO UNIVITELLINE FEMALE TWINS. ANDRÉ-THOMAS, PAISSEAU, SORREL and SORREL-DEJERINE, Rev. neurol. **67:** 567, 1937.

Two premature twins, identical in every respect, showed paralysis and amyotrophy of the neck, trunk and extremities, most marked in the supinator, triceps, brachialis and extensor muscles of the lower extremities. The proximal segments of the extremities were more involved than the distal. There were no disturbances of sensation, speech or intellect. According to the mother, the twins had developed normally until the age of 18 months, when the weakness began insidiously and progressed gradually. No similar condition could be found in other members of the family. The condition was not similar to polyneuritis, acute anterior poliomyelitis, Charcot-Marie disease or myatonia congenita. It had some resemblance to muscular atrophy of the Werdnig-Hoffmann type, but differed from this condition in several respects. The affected muscles showed an increased threshold to electric stimulation, but no reaction of degeneration. Fibrillations were absent, and muscle jerks were not obtained in response to mechanical stimulation. These features suggested that the condition was more akin to myopathy, although it did not conform to any of the known categories. Etiologically, no evidence of syphilis was found, and antisyphilitic treatment was without effect. The disease can hardly be called familial, since identical twins genetically represent one organism.

LIBER, New York.

A CASE OF IDIOPATHIC HEMIATROPHY (HUMEROSCAPULOTHORACIC TYPE) WITH ANEMIC AND TELANGIECTATIC NEVI AND HETEROCHROMIA OF THE IRIS. W. WAHL and P. CHRISTIAN, Deutsche Ztschr. f. Nervenh. **144:**1, 1937.

Wahl and Christian report the case of a boy aged 13 years with atrophy of the right shoulder. The paternal grandparents were related. Two paternal uncles suffered from progressive muscular dystrophy of the Erb type. The mother noticed when the patient was an infant that the right side of the face, ear and arm became cyanotic when bathed. At the age of 8 years it was noted that there was a difference in length of the two arms. One year later atrophy of the upper portion of the right arm and the right shoulder girdle was noted.

Examination revealed, in addition to the difference in size of the arms and shoulders, slight facial asymmetry, the left side being less developed than the right. There was a faint, bluish red telangiectatic nevus on the right cheek. The right ear was covered by many small vessels, and there were two large anemic nevi on the right side of the trunk. There were a vascular nevus in the conjunctiva of the left eye, heterochromia of the iris and a dark brown nevus constituting approximately five sixths of the iris. The authors conclude that heredodegenerative factors are the cause of the anomaly, with an inborn weakness of certain parts of the sympathetic, as well as of the parasympathetic, system as a basis.

MERRITT, Boston.

ORIGIN OF FIBRILLARY MUSCLE TWITCHINGS IN CASES OF SPINAL AMYOTROPHIES. G. GRUND, Deutsche Ztschr. f. Nervenh. **145:**99, 1938.

Fibrillary muscle twitchings in cases of amyotrophic lateral sclerosis persist even if connection between the anterior horn cells and the musculature is interrupted by lumbar anesthesia. Therefore the stimulus which causes fibrillary twitchings in this disease, and probably in the other spinal amyotrophies, does not originate from the motor horn cells. It is questionable where the stimulus for fibrillary twitchings originates. Perhaps it arises in the motor end plate, but simultaneous action of vegetative impulses can probably be assumed whenever

this symptom occurs. Vegetative fibers must be intact if fibrillary twitchings occur in the course of degeneration of the motor pathways. Epinephrine increases and physostigmine produces fibrillary twitchings. Perhaps also neurotic muscular twitching, frequently seen in the eyelids, can be explained by irritation of the vegetative nervous system.

ADLER, Boston.

GENETIC RELATIONS OF MYOTONIA, MUSCLE CRAMPS AND MYOKYMIA. G. GRUND, Deutsche Ztschr. f. Nervenh. **146**:3, 1938.

Grund reports the cases of 2 brothers with a muscular disorder which started in early adult life. The picture was largely one of atrophic myotonia, complicated by sensory changes of a peripheral type and myokymic muscular unrest and cramps. The disease was classified therefore as "neuromuscular atrophy." Grund suggests the origin of the myokymia, as well as of fibrillary twitchings associated with amyotrophic lateral sclerosis, in some vegetative influence on the motor end plates. In true myotonia the site of the lesion is elsewhere in the vegetative system, without damage to the end plate.

HOEFER, Boston.

Encephalography, Ventriculography and Roentgenography

TUMOR OF THE BRAIN WITH NORMAL ENCEPHALOGRAM. N. SAVITSKY and M. B. BENDER, Am. J. M. Sc. **194**:96 (July) 1937.

Nine cases of tumor of the brain in which the aerograms were normal are reported. Seven were taken from a series of 500 cases of verified tumor of the brain, in 120 of which there were intracranial injections of air. In 3 cases the tumor was in the parietal lobe; in 4, in the frontal lobe; in 1, in the corpus striatum and temporal lobe, and in 1, in the basal ganglia. Normal ventricular and subarachnoid systems may exist in cases of tumor of the brain, irrespective of the nature and location of the tumor and the duration of symptoms. In all 9 cases the clinical signs were sufficient for the localization and diagnosis of tumor.

MICHAELS, Boston.

AIR MYELOGRAPHY: SUBSTITUTION OF AIR FOR LIPIODOL IN ROENTGEN VISUALIZATION OF TUMORS AND OTHER STRUCTURES IN SPINAL CANAL. B. R. YOUNG and M. SCOTT, Am. J. Roentgenol. **39**:187 (Feb.) 1938.

Young and Scott have used subarachnoid injections of air since January 1936 in the study of any patient suspected of having a tumor of the spinal cord or any other space-taking lesion of the spinal canal. Their studies emphasize the accuracy of the method; in each of 13 patients the exact level of the lesion, demonstrated by air myelography, was verified by laminectomy. The efficacy and simplicity of the procedure cannot be doubted when a complete block exists. Practically, it amounts to a lumbar puncture, with injection of a few cubic centimeters of air and roentgenographic examination of the spine with the patient in the sitting posture. The trapped air is easily visualized on the roentgenogram, and the level is thus established. The lumbocaudal sac is easily filled with air and is clearly delineated. Herniations of the nucleus pulposus (or cartilaginous disk) may be discovered if this is done; so there is no reason for the use of iodized oil for this condition unless air studies reveal nothing abnormal. The diagnosis of partial block entails no more work than does a complete block if sufficient air is trapped below the obstruction to visualize it; if the air passes into the cranium it is still possible to visualize the lesion at another sitting by replacement of spinal fluid with air through cisternal puncture with the patient in the Trendelenburg position. There is practically no pain or untoward effect when from 3 to 6 cc. of air is used. When a large amount is used to outline the lumbosacral sac or the entire spinal canal, the patient should be kept in the Trendelenburg position (from 20 to

30 degrees) for six hours and flat on the back for twelve hours, and should be gradually elevated to the erect position during a period of forty-eight hours. If this procedure is followed, little headache results. It is not essential that roentgenograms be taken immediately after the injection of air if the patient is kept in the Trendelenburg position, as air has been found in the subarachnoid space below a complete block for as long as one week after injection.

CLOSED VENTRICULOGRAPHY. E. FRETSON SKINNER, Lancet **2**:903 (Oct. 16) 1937.

Skinner suggests a ventriculographic procedure with use of a hand drill, similar to that described by Sir James Purves-Stewart in 1925. The technic described has been in use for ten years. The apparatus consists of an ordinary dental drill to which has been fitted special drill pieces. These drills are lance pointed and make a hole 1 mm. in diameter. In addition, a cannula, 8 cm. long, with a tap is employed, to which may be fitted a trocar ¾ inch (1.9 cm.) longer than the cannula.

The site is shaved and aseptically prepared. The posterior approach described by Keen and Jenkins is based on Reid's base line. The site chosen ranges from 1¼ to 2 inches (3 to 5 cm.) above and from 1¼ to 4 or 5 inches (3 to 10 or 12.5 cm.) behind the center of the auditory meatus. The author recommends the orthodox landmark from 3 to 4 cm. anterior to the external occipital protuberance and from 3 to 5 cm. lateral to the sagittal line. The drill is inclined forward and inward, and the cannula enters the vestibule of the ventricle at a depth of from 5 to 7 cm. One ventricle is tapped, and "a reasonable amount of air is introduced." The head is then rotated, and air is allowed to enter the other ventricle. The cannula is withdrawn when "sufficient air has been put into the ventricles," and the wound is covered by a collodion dressing. If additional air is necessary after examination of the roentgenogram, the cannula is inserted into the opposite ventricle.

The anterior approach is the easier, but the posterior is used first because of the size of the ventricular vestibule. The site of drilling taken in the anterior approach is from 4 to 5 cm. lateral to a point on the sagittal line which lies from 4 to 5 cm. anterior to the midpoint of the distance from the nasion to the external occipital protuberance.

KRINSKY, Boston.

NORMAL VENTRICULOGRAMS IN TUMORS OF THE CEREBRAL HEMISPHERES. J. PENNYBACKER and S. P. MEADOWS, Lancet **1**:189 (Jan. 22) 1938.

Normal ventriculographic findings may be encountered in cases of infiltrating gliomas of the cerebrum. Pennybacker and Meadows report 4 cases in which focal signs and symptoms were present, with no elevation of spinal fluid pressure. In these cases the ventriculographic findings were normal. In only 1 case was operation performed. In 1 instance the lesion might have been discovered if the ventriculographic examination had been repeated. At necropsy, a tumor was observed in the parietal lobe in 2 cases, in the frontotemporal lobe in 1 case and in the frontal lobe in 1 case. The neoplasm in 1 case measured 3 by 3 by 2 cm., and the largest, 6.5 by 4.5 by 3.8 cm. On histologic examination the tumor was diagnosed as astrocytoma in 2 cases and as spongioblastoma in the other 2. Apparently the size, site and pathologic type of the cortical neoplasm do not vitiate the probability of a normal ventriculogram. The presence or absence of edema about the tumor may account for some displacement of the ventricles. A small meningioma far removed from the ventricles may produce an extreme degree of distortion by displacing the brain in front of it, whereas a small glioma near the ventricle may show no derangement in the normal roentgenographic appearance. The authors stress the importance of recognizing ventriculographic examination as merely a laboratory adjunct to the development of the clinical picture.

KRINSKY, Boston.

PNEUMOGRAPHIC STUDY OF TUMORS OF THE LATERAL VENTRICLE. H. ASKENASY, Presse méd. **45**:1576 (Nov. 6) 1937.

Askenasy points out that ventriculography with injection of air, that is, pneumography of the cerebral ventricles, is chiefly the work of Dandy and that this method has greatly modified the diagnosis, therapy and prognosis of tumors of the lateral ventricle. On the basis of his own experience with this method, Askenasy says that from the characteristics of the ventriculogram it is possible to distinguish a primary intraventricular tumor from a tumor that has invaded the lateral ventricle secondarily. In the case of primary intraventricular tumors it is necessary to differentiate between neoplasms situated at a distance from the interventricular foramen and those located near this foramen. The former determine exclusion of the part of the ventricle which is located back of the tumor, and this closed cavity is the site of considerable dilatation. Tumors of the second type, those located near the interventricular foramen, cause hydrocephalus which involves the entire ventricle of the diseased side. These, however, do not generally cause marked deformation or displacement of the lateral ventricle. In the case of extraventricular tumors which cause external stenosis of the interventricular foramen (meningioma of the small wing of the sphenoid or temporal glioma), the ventricular hydrocephalus is located on the healthy side, whereas the lateral ventricle on the diseased side is collapsed by the cerebral edema. Secondary intraventricular neoplasms do not cause interruption of continuity in the image of the ventricle of the diseased side. The external wall of the ventricle is deformed by a mass coming from outside, and the hydrocephalus, if it exists, is always much less marked than that in the case of primary intraventricular tumor.

EDITOR'S ABSTRACT.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

TRACY J. PUTNAM, M.D., *Presiding*

Regular Meeting, March 17, 1938

PATHOGENESIS OF SYPHILITIC OPTIC ATROPHY. DR. SAMUEL H. EPSTEIN.

The pathogenesis of syphilitic optic atrophy has been the subject of discussion for many years. The evidence has accumulated from two points of view: namely, the distribution of the atrophy and the pathoanatomic changes in the visual pathways. The older view that optic atrophy depends on primary degeneration of neurons either in the retina or in the nerve has not been supported by more recent work, which may be said to date from Stargardt's paper in 1913. He observed the earliest changes in the chiasm and the intracranial portion of the optic nerves, with evidence of inflammation in the pial investment of the nerves and some gliosis of their superficial parts. Behr subsequently concluded that the primary change is an inflammatory process in the connective tissue septum of the intracranial portion of the nerve and of the blood vessels in relation to it. The discovery by Igersheimer (*Ergebn. d. allg. Path. u. path. Anat.* **21**:34, 1927-1928) of spirochetes in the sheaths of the optic nerve in a large proportion of cases of syphilitic optic atrophy gave a severe blow to the theory of a metasyphilitic toxic process, and since there has been general agreement that the degeneration in the fibers of the optic nerves is secondary to syphilitic inflammation of the pia mater surrounding it. There can be no doubt that meningeal inflammation, affecting first the superficial fibers of the optic nerve in their intracranial course, gives an adequate explanation for the concentric constriction of the visual fields which is found in most cases of syphilitic optic atrophy.

Bitemporal hemianopia, which may also be found in cases of syphilitic optic atrophy, has usually been attributed to a lesion of the chiasm. That it may, however, be caused also by lesions on the meningeal surface of the optic tracts is demonstrated by the following case.

A man aged 57 gave a history of loss of sight in the right eye twenty years previously and of progressive deterioration of vision in the left eye of three months' duration. For seven years he had been troubled with shooting pains and paresthesias of tabetic type. Examination revealed that the right eye was blind and that with the left eye he could see only fingers directly in front of him. The right optic disk was flat and dead white, and the retinal vessels were very small. The left optic disk was also flat and pale, but was less affected than the right. The field of vision of the left eye showed temporal hemianopia, with sparing of at least a part of the macula, and great constriction of the peripheral field in the nasal half. The pupillary reactions were of the Argyll Robertson type. The deep reflexes in the right arm were greatly diminished and were absent in the left, but the knee and ankle jerks were present. Sensibility to pain was absent almost over the entire body, except for small areas on the feet, hands and root of the neck. The reactions of the cerebrospinal fluid were of the syphilitic type.

Postmortem examination of the nervous system showed diffuse thickening of the leptomeninges, with lymphocytic infiltrations, especially at the base of the brain. There was no evidence of tract degeneration, nor were the dorsal roots appreciably demyelinated. Meningeal infiltrations were marked throughout the intracranial portion of the optic nerves, the chiasm and the optic tracts. Demyelin-

ation was almost complete in the right optic nerve, but a few myelin sheaths, associated with a larger number of axis-cylinders, persisted in the most anterior portion of the nerve. In the left optic nerve the demyelination was greatest on the surface, and the axis-cylinders were more numerous than the myelin sheaths. Behind, the right optic tract contained much fewer myelinated fibers than the left. The crossed myelinated fibers lay near the surface of the right optic tract, while in the left tract the uncrossed myelinated fibers lay against the side of the midbrain. There was no appreciable loss of fibers on their transit from the optic chiasm to the geniculate body. In the right optic tract, however, the fibers on passing backward lay fairly deep, close to the crus cerebri. Both retinas showed great loss of nerve cells and fibers.

The evidence points to chronic meningeal inflammation as the cause of optic atrophy. The inflammatory changes were much more evident in the intracranial than in the intraorbital portion of the optic pathways, and the superficial fibers in the optic nerve were first affected. By comparing these observations with Henschen's diagrammatic representation of the position of fibers from different parts of the retina, it is seen that the crossed fibers in close relation to the meningeal surface of the optic tract appeared to recede from the surface on passing backward, becoming less numerous and showing more evidence of degeneration. This is presumed to be due to the passage of toxic products of inflammation inward from the meninges. This degeneration of the meningeal surfaces of the optic tracts, by affecting only the crossed fibers from the nasal half of the retina, may thus be a factor in producing the disproportionate reduction in the temporal halves of the fields.

PSYCHOANALYTIC OBSERVATIONS RELEVANT TO THE ETIOLOGIC BASIS OF PRECONVULSIVE AURAS. DR. IVES HENDRICK.

The memories of 2 patients, which were emotionally reenacted during psychoanalysis, indicate that their auras represented vestiges of severe acute anxiety attacks which had occurred before the onset of convulsions, and that a close relation existed between the repression of these anxiety attacks and the subsequent seizures. The aura of 1 patient consisted of a many-colored, dazzling light, apparently coming from the right. The angle corresponded exactly with that between a door and a vase refracting many-colored lights. At the age of 15 the patient had fallen in love with a teacher; his studying was disturbed by erotic fantasies of her; he had felt his eyes pulled from the vase to his mother behind the door, and he had suddenly had violent anxiety and the hallucination which later became the aura. In the second case the aura was a vestige not of the perceptual experience but of the sensation of anxiety and consisted of a "shuddering" sensation in the epigastrium. It represented the vestige of a severe acute anxiety attack which had preceded the development of seizure symptoms. In both cases there was consistent correlation between the anxiety attacks and the precipitating conflict and similar attacks in childhood. The signs in the first case were typical of grand mal epilepsy; those in the second consisted of loss of consciousness accompanied by peculiar automatisms and followed by nearly complete amnesia. Medical, physical, encephalographic and laboratory findings were irrelevant.

The role of anxiety and other emotional crises in the immediate precipitation of individual seizures is recognized. My data suggest that there is also an etiologic relationship between the whole history of seizures and antecedent anxiety attacks and that this has not been recognized because these attacks could not be remembered until the amnesia for them was resolved by psychoanalytic technic. The question of the correlation between these data on subjective experience and objective studies of cortical physiologic changes is raised. The electroencephalogram shows what happens in the cortex; my data suggest that there is a precipitating autonomic crisis which is not yet registered by this or other laboratory

methods, that inhibition of the release of this autonomic tension as an anxiety syndrome precedes the cortical explosion and that the aura, at least in these cases, represents a survival of the preepileptic anxiety attacks.

LOCALIZATION OF CEREBRAL LESIONS BY ELECTROENCEPHALOGRAPHIC EXAMINATION. DENIS WILLIAMS, M.R.C.P., London, England.

The paper of which this is a preliminary report will appear in a later issue of the ARCHIVES.

TRACY J. PUTNAM, M.D., *Presiding*

Regular Meeting, April 21, 1938

RELIEF FROM UNILATERAL PARALYSIS AGITANS BY SECTION OF THE PYRAMIDAL TRACT. DR. TRACY J. PUTNAM.

The fact that the tremor of paralysis agitans is arrested by hemiplegia was recognized by Parkinson. Recently, Bucy has demonstrated that surgical resection of the motor cortex produces the same result. Section of the extrapyramidal tracts in the spinal cord failed to abolish alternating tremor in 5 cases in which operation was performed in this clinic. The idea that the tremor should be relieved by section of the pyramidal tract suggested itself, and watch was kept for several years for a case in which unilateral tremor was sufficiently severe to justify the disability which might be expected. Such a case appeared recently.

CASE 1.—Lillian C., aged 32, had suffered for seventeen years from paralysis agitans of the right side, of sudden onset. During this period she had been entirely incapacitated and unable to use her right hand for writing, eating or doing her hair. She also had tremor of the right leg and a curious high-stepping gait. The tremor had grown slowly worse.

On examination it was found that she had weakness and slight rigidity of the right arm and leg. The Babinski phenomenon was present. The mental level was rather low.

After trial of the usual medical treatments for several months, the patient begged for some operation to relieve the tremor. When the risks were explained to her she eagerly assented to the procedure. The operation was performed on March 4, 1938. The right lateral pyramidal tract was sectioned at the level of the third cervical segment to a depth of 5 mm. and for a width of 3 mm.

The patient has been free from gross tremor since the operation, though a fine tremor is still perceptible at rest. The strength of the hand is essentially the same as before operation. She can move the thumb and fingers individually and can write, hold a glass of water and fasten buttons with the right hand. Walking is moderately improved. Rigidity has disappeared. The deep reflexes are somewhat more active than before the operation; no new pathologic reflexes have appeared.

CASE 2.—Thomas R., a laborer aged 52, for five years had had an alternating tremor of the left hand, which was gradually increasing. There was also trifling tremor of the left side of the face and neck and the left leg. The left hand was weak, but could be used; however, the coarse tremor was so tedious and annoying that he hesitated to seek work. The Wassermann reaction was positive; the patient was given treatment, without effect on the tremor. Large doses of scopolamine, stramonium, cobra venom and diphenylhydantoin were given, without benefit. After having talked with the patient in case 1, he requested an operation.

On April 7, 1938, left hemilaminectomy was performed on the second vertebra and the lateral pyramidal tract was sectioned. This time care was taken to cut

chiefly the inner fibers of the tract, next the gray matter, over an area of approximately 5 by 2 mm.

The tremor of the hand and leg was completely relieved, though that of the face continued. The strength of the hand was essentially as before. The strength of the leg was not affected, and the patient walked eight days after the operation. Movements of individual joints and fingers were possible. There was no tremor in the finger to nose test and no rigidity. The deep reflexes became somewhat more lively. The Hoffmann sign was not obtained; the Mayer sign was present. The left abdominal jerk was absent. The Babinski, Oppenheim and Barre phenomena appeared. There was slight analgesia of the radial side of the right hand, which rapidly disappeared.

Moving pictures of both patients before operation and the patients themselves are presented.

ELECTROMYOGRAPHIC STUDIES IN SPASTIC CONDITIONS AND IN PARALYSIS AGITANS. DRS. PAUL F. A. HOEFER and TRACY J. PUTNAM.

It has been the purpose of the present investigation to study action potentials arising from human muscles of persons with certain motor disorders and to correlate them, if possible, with physiologic and pathologic conditions of the central nervous system. Studies on 49 patients are presented; about 400 records were taken with a cathode ray oscillograph or, in some instances, with a six channel electroencephalograph and ink-writer for simultaneous tracings. In addition, records from normal subjects were taken under comparable conditions as controls. In patients with spastic conditions clonus, direct and contralateral responses to proprioceptive and heteroceptive reflex stimulation and "spontaneous" activities in muscle were studied. In cases of paralysis agitans tracings were made of tremor occurring in the facial musculature, the sternocleidomastoid muscles and the extensor and flexor muscles of the arms and legs. Furthermore, responses to active and passive motion and reflexes were recorded. In both groups of patients responses arising in synergistic muscle groups, in single whole muscles and in single motor units were traced and compared. In a few experiments, also, the influence of such drugs as curare and scopolamine on tremor, clonus and voluntary muscle power was investigated, both clinically and electrically. Both clonus and tremor appeared as trains of bursts of action potential spikes in groupings which were similar for both phenomena. The rate, duration of the single burst, free interval between bursts, number of spikes in the single burst and frequency of the spikes per second were so much alike that the electromyograms for tremor and those for clonus could not be distinguished. The most interesting result, however, seemed to be that both in clonus and in tremor the pattern obtained from motor unit leads and that from whole muscle or muscle group leads were identical, indicating that in both instances there is synchronization, which must be assumed to take place at a level above all lower motor neurons participating in either clonus or tremor. The frequency of impulses thus arising above the anterior horn cells and reaching the motor units was from 280 to 400 per second in a number of instances in which analysis was made. The normal frequency of impulses from a single motor unit has been reported to be from 5 to 90 per second, while the lower neuron, according to its refractory period, is able to carry 2,000 impulses per second. It is justifiable, therefore, to assume that in both clonus and tremor the normal flow of impulses is modified by the influence of structures the character and location of which are still unknown, probably in the spinal cord. In spastic conditions there was found reflex irradiation with a "spastic" reflex action potential, i. e., one consisting of several spikes and after-discharges, whenever the reflex spread from a diseased to a normal area, and with a normal reflex action potential, i. e., one of single spike structure, when reflexes spread from a normal area. It was found that reflexes can spread upward and downward, to the contralateral side or on the same side, even on the normal side in hemiplegic patients. After-discharge and a more complex structure of

the reflex action potential pattern were also seen in patients suffering from paralysis agitans, but no spread of reflexes was seen in these persons or in normal subjects serving as controls. A tremor pattern may be superimposed on voluntary or involuntary motion in cases of paralysis agitans; in some instances the tremor pattern replaced the normal even flow of innervation. Generalized tremor was found to be surprisingly synchronized in all the areas involved. While the intensity of the tremor may shift continuously both clinically and electrically, the rhythm was found to be uniform to a surprising degree in simultaneous leads and, with only 1 exception, in successive observations over several weeks and months. Curare depressed both tremor and clonus and in proper doses did not paralyze normal voluntary motion or respiration. The findings in cases of spasticity and in those of paralysis agitans are compared and commented on with a discussion of hypothetic structures which may be the carriers of both groups of phenomena. Physiologic observations on conduction and distribution and "reverberation" of impulses, surgical experiences in section of tracts or resection of cortical areas and clinical observations, such as the disappearance of tremor not only after hemiplegia but also during a high degree of voluntary activity, are considered. The number of questions raised by this investigation greatly exceeds the number of conclusive and satisfactory explanations at present available.

Treatment of Chronic Alcoholism with Benzedrine: A Preliminary Report. Dr. Wilfred Bloomberg.

Ten cases of chronic alcoholism are reported in which the patients have been treated with benzedrine sulfate during the past year. Encouraging results were obtained in over half of the patients, with complete elimination of the alcohol intake in several instances. It is suggested that the drug acts by relieving depression and supplying a "lift," during which alcohol is no longer necessary. It is concluded that the treatment offers a promising means of producing a latent interval of sobriety, during which psychotherapy may be inaugurated.

Enuresis and Other Factors in Normal and in Psychotic Persons: A Comparative Study of Incidence and Intercorrelations. Dr. Joseph J. Michaels and Sylvia E. Goodman.

This paper appeared in the October issue of the Archives, page 699.

PHILADELPHIA NEUROLOGICAL SOCIETY

J. C. Yaskin, M.D., *President, in the Chair*

Regular Meeting, April 22, 1938

Minor Injuries of the Cervical Segment of the Spine and Their Consequences. Dr. Alfred Gordon.

In the large majority of recorded cases of injuries to the cervical portion of the spine there is gross damage, namely dislocations or fractures of the vertebrae with secondary gross lesions in the spinal cord, leading to muscular atrophies or spastic paralysis of the extremities as the result of degeneration of tracts, as well as to involvement of the sphincter of the bladder or to persistent priapism in men. Cases of less severe damage are not common and are frequently not recognized. In such cases the symptoms referable to the cord are slight at first; the moderate degree of the initial disability is looked on with no special concern, and the prognosis for complete recovery is ordinarily favorable. Nevertheless, close and prolonged observation will reveal that the apparently mild disturbances

have as a basis serious lesions in the cord. As an example of such apparently minor lesions which demand recognition and serious consideration, the following case is reported.

REPORT OF A CASE

P. M., aged 50, a laborer, was thrown from a wagon in October 1936; the vertex of his head struck the ground, producing excessive anterior flexion of the cervical portion of the spine. There was no loss of consciousness; he was merely "dazed." During the following two weeks there was gradual development of pain in the neck and weakness in both arms. The patient was admitted to the Coatesville Hospital, where the head was immobilized in an apparatus for eight weeks. After removal of the latter the patient was unable to move the head in any direction and could not raise the left arm above the shoulder; he also observed muscular twitchings in both arms.

Roentgenologic examination of the cervical vertebrae at that time showed no fracture and no dislocation, but the intervertebral space between the sixth and the seventh vertebra was a little wider on the right side than on the left. The neck was rigid, and flexion, extension, rotation or lateral movements could not be obtained without considerable pain. The left arm could be raised only partially, although the shoulder joint presented no pathologic condition (the roentgenogram showed nothing abnormal, and the head of the humerus could be rotated in the cavity without difficulty). There was apparently no atrophy of the muscles of the arms, and no reaction of degeneration could be ascertained. The grip of both hands was good.

Now, the biceps and triceps reflexes on both sides at times are greatly diminished and most of the time are not elicited. By percussing the lower end of the radius on the left side one obtains sometimes slight flexion of the fingers. This is the so-called inversion of the radial reflex, which, according to Babinski (1910), is characteristic of an injury of the fifth cervical segment of the spinal cord. The third striking symptom at present in this case consists of continuous muscle waves (myokymia) and fibrillary contractions of the flexor and extensor muscles of the upper portions of both arms, more on the left side than on the right. The myokymia becomes more pronounced on mechanical irritation of these muscles. Moreover, at times simultaneously with the clonic manifestations there are sudden tonic spasms of the muscles of the forearm, but only on attempts at abrupt voluntary movements. Finally, it is observed that the scapulohumeral tendon reflex is more marked on the left side than on the right: By percussion of the middle of the inner border of the scapula there are abduction and external rotation of the entire arm, more on the left side than on the right. Sensations of all forms are normal in the upper extremities.

The tendon reflexes of the lower extremities are increased, but there are no pathologic reflexes. The sphincters have not been affected since the accident. The pupils have also been normal. The blood and urine are normal in every respect. The Wassermann reaction of the blood is negative, and the spinal fluid is normal.

There have been complete restoration of function of the cervical muscles and considerable improvement in raising the arms. The objective pathologic symptoms at present are: difficulty in obtaining tendon reflexes in the upper extremities, occasional elicitation of inversion of the radial reflex and, finally, continuous muscle waves and fibrillary contractions of the muscles of the upper portions of both arms.

The case suggests strongly an anatomic disorder in the cervical portion of the cord. The continuous wavelike muscular contractions associated with fibrillations, as well as the occasional tonic spasms, all confined to the flexor and extensor groups of muscles, speak eloquently in favor of continuous irritation of the segments of the cord innervating those muscles or of the nerves distributed to them, namely, the musculocutaneous and the musculospiral nerves, which originate in the fifth and the seventh cervical segment, respectively. Moreover, if

one recalls the presence (although not constant) of inversion of the radial reflex on the left side, which, according to Babinski, is due to damage of the fifth cervical segment, one is fortified in the assumption that the condition in the case under consideration is due to an anatomic disorder in the cervical portion of the cord. Babinski also found that abolition of reflexes in the upper extremities indicates a lesion in the cord extending from the fifth to the eighth cervical segment.

As to the nature of the lesion in this case: It cannot be destruction of the cells of the anterior horn, as there would have been muscular atrophy and flaccid paralysis, which are not present. The myokymia here is incessant and continuous. The motor phenomenon is therefore probably due to equally incessant and continuous irritation of the cells of the anterior horns or of the anterior roots. The motor disturbance developed soon after a brief preliminary period of paralysis of both upper extremities, following forced flexion of the head.

DISCUSSION

DR. ROBERT A. GROFF: Dr. Gordon has presented an interesting problem regarding the association of fibrillary tremors and injury of the cervical portion of the cord. As far as I know, and I believe that I am correct, the literature does not contain the report of any case such as he has described this evening.

I am not quite convinced that the evidence he has at hand is sufficient to say that this patient sustained an injury to the cervical portion of the cord. Walsh and Ross described atrophy of the small muscles of the hand as well as diminution in the biceps reflexes and inversion of the radial reflex. They did not describe fibrillary tremors associated with the injuries that they saw.

Myokymias may be divided into two categories—those that are alleged to be due to various causes, such as fatigue or neurasthenia, and those which are due to disease of the anterior horn cells. Myoclonias fall in a different class and are probably of more central origin. It will be interesting to see what becomes of this patient in the future.

DR. MILTON K. MEYERS: I believe that the problem of fibrillary contractions and their relation to trauma, with the possibility of disease of the anterior horn cells, has not been fully settled. There are a number of cases reported in the literature in which amyotrophic lateral sclerosis followed trauma and began in the muscles affected by the trauma.

Such a case came before a referee board, and two distinguished neurologists of Philadelphia testified against the interests of the plaintiff. The lawyer for the plaintiff was not satisfied with the opinion of the referee, which was adverse to his client; having heard of a well known neurologist in New York who was acquainted with the literature, he wrote for his opinion. The New York neurologist replied that the Philadelphia neurologists had erred when they stated that no such cases had been reported in the literature. He came to Philadelphia, testified at the appeal trial and helped to win a verdict for the family of the injured man, who had died in the interim.

I have with me part of the report of a case in which fibrillary tremors were present at the site of an injury, although they were not confined to that site. The case was that of a man who had one shoulder injured in December 1937; now the muscles of both shoulders show fibrillations.

When the patient was first seen the deltoid muscles, the muscles of the shoulder girdle and back and the pectoral muscles showed fibrillary twitchings. No such movements were then noted in the forearms and hands. Pain and tactile sensation were not disturbed. The biceps reflexes were somewhat increased, but Trömner's sign was absent. The reflexes in the lower extremities were normal except for a diminished achilles jerk.

It was believed, in view of the fibrillary twitchings, that the possibility of amyotrophic lateral sclerosis or tumor of the spinal cord or spinal canal was to be considered. The last two conditions were excluded by the lack of pronounced objective sensory changes.

Subsequent examination revealed fibrillary tremors also in one muscle of the hand on the side opposite that of the injured shoulder. This hand had been injured several years previously, and the muscle that showed fibrillations has been wasting.

Although the cause of amyotrophic lateral sclerosis is not known trauma seems to play a part in some of the cases.

DR. A. M. ORNSTEEN: I am interested in knowing what happened originally to the man whose case has been reported tonight. From the report, I gather that he had weakness of the shoulder girdle but not of the hand.

Vascular changes, such as hemorrhage and swelling in the cervical nerves, may be the cause of weakness following injury to the shoulder girdle. I have in mind postneuritic irritative phenomena. Whether they involve inflammatory lesions or traumatic changes in the nerves I do not think matters.

Why cannot this case be one of postneuritic irritative phenomena, particularly if there was no evidence of spinal injury at first? When there has been no fracture of the vertebrae but a strain on the cervical portion of the spine, injury of the spinal cord is usually due to concussion or hemorrhage. In most cases I doubt whether a lesion can be ascertained from its effect on the segment alone, without all the other signs of acute shock to the cord.

DR. ALFRED GORDON: Dr. Ornsteen spoke of neuritic pain. Let me review briefly the condition in this case. The man fell with the vertex striking the ground, with resulting forced flexion of the neck. He had no pain. Pain gradually developed and was limited to the muscles of the neck. There was only weakness in the arms.

It has now been about a year and a half since the accident occurred. If the condition had been real neuritis it would have been painful, but there has never been any pain in the arms. If there had been destruction of the cells of the anterior horn, there would have been some effect on the muscles by this time, at least temporarily. The patient has a magnificent grip.

The myokymia with loss of reflexes is significant and is in agreement with the condition resulting from forced flexion of the spinal cord described in the case reported by Walsh and Ross. Minor injuries of the cervical portion of the cord should not be overlooked.

MENINGOENCEPHALITIS DUE TO CRYPTOCOCCUS HOMINIS (TORULA HISTOLYTICA): REPORT OF A CASE.

DRS. J. G. GREENFIELD, London (by invitation), and MATTHEW T. MOORE.

Invasion of the central nervous system by Cryptococcus hominis (Torula histolytica) appears, from the number of cases reported in the literature, to be rare. This probably is more apparent than real, for, as many observers have stated, the clinical course of meningitis or meningoencephalitis due to C. hominis is similar in many respects to that of tumor or abscess of the brain or tuberculous meningitis. It is probable that many cases in which the diagnosis was chronic tuberculous meningitis or abscess of the brain and in which careful studies of the cerebrospinal fluid and necropsy were not carried out may have been those of cryptococcic infection; indeed, the diagnosis is sometimes made unexpectedly after histologic examination of the meninges and brain.

Dr. J. Purdon Martin, of the National Hospital, Queen Square, London, gave us permission to report this case.

REPORT OF CASE

History.—C. C., a youth aged 18, a clerk, was admitted to the hospital on Dec. 14, 1936, with the complaint of headache, giddiness, vomiting, pain in the neck, impaired vision and infection of the right hand.

Four weeks before entering the hospital, he struck the right index finger on the corner of a table and produced a minor abrasion. This healed, forming a

scab, and he paid no attention to the injury. About five days later he experienced a constant dull pain across the forehead, which came on toward evening, and on awakening the following morning the headache was still present. One week after the injury to the finger, and at a time when the frontal headache was very severe, he noticed that the injured finger had become swollen to about twice its normal size and was very painful. Within a few days the back of the hand was swollen, and there was pain in the right axilla. For the first time he began to feel sick and vomited several times. He then began to suffer from giddiness whenever he turned his head quickly or sat up. At about this time he began to have pain and stiffness in the back of the neck and blurred vision. Symptoms became steadily worse, and he was admitted to the Bolingbroke Hospital, London, ten days before his admission to the National Hospital. During that time the pain in the neck became much worse and extended downward between the shoulders. He had double vision for a short time.

The family history and the past medical history were irrelevant.

Examination.—Examination revealed a tall, thin youth who did not appear acutely ill. He was alert, intelligent and cooperative. There was no disturbance in speech or memory. On admission the temperature was 97.4 F., the pulse rate 64, the respiratory rate 20 and the blood pressure 115 systolic and 65 diastolic. The temperature varied from 97 F. to normal until December 24, when ventriculographic examination was performed. After this it remained above normal, but never rose above 101.4 F. Prior to the ventriculographic procedure, the pulse rate varied from 48 to 84, the average being about 56. After ventriculographic examination and craniotomy the pulse rate rose as high as 104, with an average of 88.

There was no disturbance in olfaction. The fields of vision were full except for large blindspots. There was papilledema of 2 diopters in each disk. The retina was edematous, and many large and small hemorrhages appeared along the vessels near the disks. The remaining cranial nerves were normal. Motor function was normal throughout. The reflex activity was normal except for questionable plantar flexion on both sides. Sensation in all forms was preserved and readily appreciated. Meningeal signs were manifested by a moderate degree of rigidity of the neck and a weak Kernig sign. There were two or three enlarged, soft glands in the right axilla, but the lymph glands elsewhere were normal. An ulcerated area over the dorsum of the second phalanx of the right index finger was discharging a considerable amount of thick, yellow pus.

Lumbar puncture, performed on December 5 in the Bolingbroke Hospital, revealed a pressure of over 300 mm. of water. The cerebrospinal fluid was clear, and laboratory examination showed 37 cells per cubic millimeter, 35 of which were lymphocytes, 0.04 Gm. of protein and 750 mg. of chlorides per hundred cubic centimeters. There was no pellicle on standing, and no tubercle bacilli were seen; the culture was sterile. While the patient was in the Bolingbroke Hospital, a tentative diagnosis of cerebral abscess was made.

Lumbar puncture on December 15 showed a pressure of 300 mm. of water; clear, colorless fluid; 2 cells; a total protein content of 0.07 Gm. per hundred cubic centimeters, and a negative Wassermann reaction. Ventriculographic examination on December 24 revealed symmetrically dilated lateral ventricles and a dilated third ventricle. After the ventriculographic procedure a cerebellar exploration was performed, and a localized cyst due to circumscribed adhesive meningitis was evacuated. The cerebellar tonsils and the fourth ventricle were compressed by the cystic formation. After operation the general neurologic status grew worse, and the patient died on Jan. 10, 1937.

Postmortem Examination.—The pial vessels were congested diffusely over the brain. There was some adhesive meningitis over the ventral surface of the pons and cisterna basalis. No other evidence of infection was observed.

Histologic Examination.—The meninges, particularly those forming the cisterna magna and pontis, were greatly thickened and distended by a diffuse infiltration of

cellular elements, consisting of endothelial macrophagocytes, multinucleated giant cells, lymphocytes, occasional plasma cells and numerous yeastlike organisms. The endotheial cells made up a large proportion of the meningeal infiltration. Lymphocytes did not appear in great numbers, but occasionally were grouped in clumps and with giant cells formed a granulomatous mass in the meninges. No caseation was to be seen, however. Many of the giant cells contained round or oval bodies, from 6 to 10 microns in diameter, some of which were in the process of budding. Yeastlike bodies in huge numbers appeared both free and encapsulated in the thickened meninges. These bodies were gram-positive for the most part, particularly when the capsule was intact, but many were amphophilic when they occurred free and were devoid of a capsule. They varied in size and shape and were in various stages of budding. With Gram's stain corona-like radiations or spicules were seen extending from the densely stained cell through the capsule. Many of the smaller cells, especially the daughter cells, contained refractile granules. The intact capsule enclosing the organism attained the diameter of 20 microns. The thickened meninges were remarkably free from formation of new fibrous tissue, the reticular meshwork being filled almost exclusively with cellular elements. The brain substance was irregularly studded with small perivascular infiltrations involving both the cortex and the white matter. The basal ganglia appeared to be most involved in this process. The cellular infiltration consisted of encapsulated cryptococci, endothelial cells and giant cells, which arranged themselves concentrically about a vessel, giving a cystlike appearance, or along the course of a vessel, producing a spindle-shaped arrangement. The centrally lying vessel had an intact intima and media, the adventitia apparently having been fragmented and distended by the invading cryptococci.

The majority of the cryptococci present in the perivascular spaces were surrounded by a capsule, which with the toluidine blue stain appeared as dark-staining central bodies, from about 10 to 12 microns in diameter, surrounded by a clear halo. Although cryptococci were in the majority, endothelial cells and numerous multinucleated giant cells constituted the remaining infiltrating elements. Immediately surrounding the cystlike formations, the brain tissue showed little, if any, reaction, the appearance of reaction being intimated by tissue compression. Ganglion cells lying adjacent to the lesions showed no disturbance in morphologic or staining characteristics. The cortex, except for an extremely mild subpial reaction, showed no changes. The vessels not involved by invasion of cryptococci were in the main normal. A small area in the white matter of the occipital lobe showed hemorrhage, with surrounding softening and numerous gitter cells. This area corresponded to the track of the ventricular puncture.

Comment.—Cases of yeastlike infection of the central nervous system have been reported in many lands, the United States heading the list with the majority. The case described here is the second to be reported in England; as in the first, the diagnosis was established by histologic examination of the meninges and brain.

The emphasis laid by the majority of authors on the misleading similarity of cryptococcic infection of the central nervous system to tuberculous meningitis and tumor and abscess of the brain is borne out in this case. The bradycardia and subnormal temperature observed in this case in association with the subjective complaints, absence of definite localizing neurologic signs, increased intracranial pressure and the findings in the cerebrospinal fluid made the presumptive diagnosis of abscess of the brain warrantable. Moreover, the ventriculograms, which showed uniform dilatation of the lateral and third ventricles, indicated a compressive lesion in the posterior fossa. The cerebrospinal fluid showed no organisms, and the cultures were sterile. Johns and Attaway emphasized the importance of examining the cerebrospinal fluid with the oil immersion (1/12) objective instead of the 16 mm. objective; otherwise the organisms may be missed. It may be well in all questionable cases to inject the cerebrospinal fluid intracisternally into laboratory animals. In this way, the organism if present can be recovered in pure culture, and the lesions in the central nervous system can be reproduced for diagnosis.

The subjective complaints of the patient, beginning with headache and followed by giddiness, vomiting, pain in the neck, impaired vision and diplopia, were characteristic of cryptococcic infection.

The sequence of events, consisting of an abrasion of the skin, swelling of and pain in the hand, swollen axillary glands and symptoms of increased intracranial pressure, was more than a coincidence. The broken skin in this case may well have been the portal of entry for C. hominis.

That several strains of C. hominis of varying degrees of virulence exist is illustrated by the 2 cases cited by Todd and Herrmann, in 1 of which the patient presented evidence of involvement of the central nervous system for two years, with the condition remaining stationary and with cryptococci present in the cerebrospinal fluid during all that time.

Summary and Conclusions.—1. A case of meningoencephalitis due to C. hominis is described.

2. The suggestion of adopting a final terminology based on acceptable nosologic usage is offered.

3. The portal of entry in this case was in all probability through the broken skin.

4. Attention is drawn to the necessity of performing detailed bacteriologic studies on the cerebrospinal fluid in doubtful cases of chronic meningitides and intracranial space-taking lesions.

DISCUSSION

Dr. Michael Scott: Dr. Greenfield and Dr. Moore have given an interesting presentation, which brings to my mind a case which occurred in Dr. Temple Fay's service about a year and a half ago. The patient gave a history of having had an operation, in an institution in another state, for suspected tumor of the brain. At that time a decompression was made in the right temporal region, but no tumor was seen. Apparently a discharging fistula developed in this area, and the patient was finally sent to the Temple University Hospital.

On admission the patient had a subnormal temperature and slightly clouded mentality. Examination of the spinal fluid showed an increase in the protein content, the pressure and the number of lymphocytes. The question arose whether the patient had an abscess of the brain; at operation Dr. Fay observed in the right temporal lobe and extending into the frontal lobe three or four completely encysted sacs, which had made pockets in the brain substance. When these were removed, multilocular pockets were left in the brain. Three days after operation meningitis developed and the patient died. The organism was found to be Cryptococcus. In this case, therefore, the patient had been treated previously for a tumor of the brain, but final analysis showed that he had abscess of the brain due to Cryptococcus.

Dr. Matthew Moore: Several important problems have been raised concerning diagnosis and, that which is of particular interest, treatment. I believe that the important factor in regard to treatment lies in establishing a differential diagnosis in doubtful cases, for appropriate treatment of tumor or abscess of the brain or of amenable meningitides may result favorably. The means by which this condition can be ascertained, as in the case cited by Neill and Shapiro, in which the diagnosis was made ante mortem and no postmortem study was made, is injection of the cerebrospinal fluid intrathecally into guinea pigs. When this is done, the organism can be obtained in pure culture within a comparatively short time; furthermore, reproduction of the characteristic lesions of the brain occurs, which can be studied histopathologically.

It is interesting, apropos of Dr. Scott's case, that many cases of meningitis due to C. hominis have been mistaken for those of tuberculous meningitis. I recall, as an intern, having 3 cases within two months in which the condition was diagnosed as tuberculous meningitis. In 1 case, that of a young girl, repeated reports

were received from the laboratory that the cerebrospinal fluid culture was negative but that there was contamination with yeastlike bodies of the various specimens submitted for study. That is the characteristic finding. Frequently, in cases which have been recorded, the laboratory report has stated that there was contamination with yeast. The pathologist unwittingly has made the diagnosis. As far as abscess is concerned, the usual picture is one of subnormal temperature and bradycardia; thus, in the present case the pulse rate of 46 and the associated findings could easily have been interpreted as indicative of an abscess of the brain.

There is no known satisfactory treatment. The only case reported in which the patient was living is that reported by Todd and Herrmann, in which the organism was present in the cerebrospinal fluid for two years.

SPINAL EPIDURAL LESIONS: REPORT OF THREE CASES. DR. B. A. HIRSCHFIELD, Trenton, N. J., and DR. J. C. YASKIN.

Lesions of the spinal epidural space are more common than is generally supposed and include primary and metastatic tumors, suppurative infections and granulomas, thrombophlebitis of the meningorachidian veins, extradural cysts, protrusion of the intervertebral disks and infiltrations associated with leukemia and Hodgkin's disease. Three cases are reported in which operation was performed: In the first, the lesion was primary sarcoma; in the second, metastatic carcinoma, and in the third, acute epidural abscess.

Most of these lesions, by reason of direct compression or interference with the blood supply, lead to irreparable damage to the spinal cord. Early diagnosis is, therefore, necessary, especially in cases of acute suppurative infections, in which there are rapid compression and the additional danger of inflammation of the meninges and cord.

The early symptoms suggestive of epidural lesions include pain low in the back and root pains, which are common to intradural as well as to extradural lesions. Signs of meningeal irritation were observed in a number of cases of lesions of the epidural space and are highly suggestive of that localization.

The combined occurrence of pain low in the back, root pains and signs of meningeal irritation (even before evidence of compression of the spinal cord appears) calls for inquiry as to antecedent and search for coexisting infections and other etiologic factors, as well as roentgenographic examination, manometric studies and detailed examination of the spinal fluid and, if necessary, studies of the spinal subarachnoid space by injection of iodized poppyseed oil or air. A systematic investigation of this sort, in addition to complete and repeated neurologic examinations, will in the majority of cases disclose evidences of an extradural lesion, permitting timely operative intervention.

DISCUSSION

DR. ROBERT A. GROFF: The authors are to be complimented on their comprehensive and careful review of the types of epidural lesions and their diagnostic features. The cases reported are interesting because they represent the most common conditions.

The case of the metastatic lesion in the epidural space brings up a particular problem. I have always held the view that metastatic lesions of the epidural space produce symptoms and signs more by vascular occlusion than by direct compression. Removal of the lesion, therefore, will not be attended by improvement. The authors' case supports this view, and I am sure those present have seen other cases in which there was the same turn of events.

The authors are to be complimented on the speed with which they made the diagnosis of acute spinal epidural abscess. It was exactly thirty-six hours after paralysis had set in that the patient was operated on and the abscess drained. The follow-up study of this patient showed that the rapid diagnosis and prompt institution of treatment saved him the use of his legs. The diagnosis of spinal epidural

abscess is not made early because the neurologist or internist does not think of this possibility. A patient with a history of infection, no matter what, who has a sudden boring pain in the back and shows signs of meningeal involvement should be considered as having a spinal epidural abscess, and treatment should be instituted at once.

Browder, in a discussion of spinal epidural infections, reported a case in which the operation was performed before paralysis set in. The abscess was drained, and no neurologic signs developed. Let this be a mark at which to shoot.

DR. MICHAEL SCOTT: My colleagues and I have had cases of epidural abscess in which a complete subarachnoid block was present; in 1 case the neurologic level was at the fifth thoracic dermatomere. In these cases we removed 5 cc. of fluid by lumbar puncture, with the patient sitting up, and injected 5 cc. of air. The air rose in the spinal canal, like a bubble in a mason's level, and stopped at the level of the block. Stereograms and anteroposterior and lateral roentgenograms were then taken by Dr. Chamberlain, and the bubble of air was visualized, giving us a definite localization for surgical intervention and corroborating the neurologic findings.

With regard to lesions of the lower lumbocaudal sac, especially those in which there is herniation of the nucleus pulposus: We have shown by air myelograms that during hyperflexion the herniated disk at times recedes and that on hyperextension it again herniates into the spinal canal. In other words, some herniated disks may change their location, depending on the patient's posture, and so may produce intermittency of symptoms.

These epidural lesions offer interesting problems, and there is much to be learned about them from a diagnostic standpoint.

DR. B. A. HIRSCHFIELD: In spite of the location of the lesions in the thoracic region, the patients complained of low back pain as the first symptom. I do not understand the mechanism, but this was true of 3 patients.

DR. J. C. YASKIN: I may say in conclusion that it is well known to physicians who have tried to diagnose tumors for several years that tumor in any region of the cord may be accompanied by pain low in the back. Perhaps our chief purpose in this twenty minute presentation was to call attention to the epidural space and to the fact that with certain epidural lesions meningeal irritation is a striking symptom. Some of these lesions, especially the suppurative process, are amenable to surgical treatment, if diagnosed early enough. For this reason they deserve special consideration.

CEREBRAL FAT EMBOLISM RESULTING FROM A MINOR INJURY TO THE LOWER EXTREMITIES. DRS. ALEXANDER SILVERSTEIN and FRANK KONZELMANN (by invitation).

The purpose in describing this case is to call attention to the well established clinicopathologic syndrome of cerebral fat embolism, which has been almost entirely neglected by American neurologists and neuropathologists. We emphasize that we are reporting not a curiosity observed post mortem but a fairly frequent neurologic syndrome that may prove of practical importance. That trauma to the extremities, not necessarily fracture of a bone, can produce profound cerebral symptoms due to specific pathologic changes in the brain is a fact that cannot be stressed too strongly and, we believe, is worthy of careful investigation and study. The medicolegal implications are self evident.

The literature on fat embolism is voluminous. There are more than 500 references, dealing with every phase of the problem. Our case illustrates graphically how even the correct pathologic diagnosis can readily be missed unless one bears this complication in mind. The correct diagnosis of cerebral fat embolism was made more than one year after careful histopathologic studies had been concluded. Dr. Mona Spiegel-Adolph and Dr. Ernest Spiegel suggested and verified the diagnosis of cerebral fat embolism.

REPORT OF CASE

An apparently healthy, strong, athletic youth aged 19 sustained what was thought to be a minor injury to the lower extremities. Two hours after the injury he suddenly became unconscious; decerebrate posture with tonic fits developed, and he died about five days after the onset. Necropsy revealed severe edema of the brain, numerous coagulated necrotic areas, punctate hemorrhages, fat globules in the vessels and other changes seen in cerebral fat embolism.

When the patient was first examined, it was imperative that a prompt decision be made as to the nature of the lesion, particularly as to the advisability of surgical intervention as an emergency. In view of a history of mild trauma to the head four weeks prior to the accident, the possibility of a preexistent subdural hematoma had to be ruled out. Furthermore, a history of severe headaches suggested the possibility of a latent tumor of the brain. The normal spinal fluid pressure and the absence of choked disks, however, were against the possibility of a "space-occupying" lesion. The decerebrate picture, the severe vegetative disturbances, such as elevation in temperature, the hyperglycemia (with no glycosuria) and the respiratory and cardiac disturbances were all evidences of a severe intracerebral lesion implicating mainly the basal ganglia and the brain stem. The condition was thought to be due to severe edema of the brain with multiple petechial hemorrhages. Sunstroke was considered one of the etiologic factors.

Necropsy by Dr. Konzelmann revealed, in brief: acute pulmonary abscess, suppurative bronchopneumonia and passive congestion; acute glomerulonephritis; passive congestion of the liver, and persistent degeneration of the thymus with calcification of Hassall's corpuscles.

Gross observations of the brain showed a moderate increase in the cerebrospinal fluid. The brain appeared large and edematous. The convolutions were slightly flattened, and the sulci were shallow. Incision of the brain revealed numerous small petechiae, which appeared to be in clumps. They were seen mostly throughout the cortex and in the basal ganglia, pons, medulla and midbrain.

The microscopic diagnosis by Dr. Winkelman was: (1) purpura of the brain, (2) severe endarteritis, (3) multiple areas of coagulation necrosis and (4) severe toxic cerebritis.

Additional microscopic examination by Dr. Konzelmann and Dr. Ernest Spiegel with specific fat stains, such as osmic acid, scarlet red and sudan III, revealed numerous fat emboli in the capillaries and smaller blood vessels. These could be seen as small oval globules, sometimes occupying the entire lumen of the vessel and occasionally breaking through the wall of the vessel. The fat emboli were most numerous about the rarefied areas and in some instances could be seen plugging the lumen of the vessels in the central necrotic area of the ring hemorrhage.

Comment.—The etiologic factor in this case appears to have been a sudden jarring of the skeleton, which occurred when heavy steel tanks struck the lower extremities; an additional factor may have been multiple contusions in the lower limbs. It is of interest to note that the factor of jarring, or *Erschütterung*, is a not infrequent cause of fatal fat embolism; cases have been reported by leading pathologists, such as Virchow, Ribbert, Schmorl, Ziemke and Beitzke. That systemic invasion of fat is more likely to occur in young, strong persons with strong myocardial musculature is a fact that was first demonstrated by Grøndahl and verified by other observers; it is further substantiated by our case, the patient being unusually robust and athletic. A patent foramen ovale was not observed.

In the clinical picture there were several signs the significance of which was not recognized but which have been emphasized in the reports in the literature as characteristic of the condition: The first was the free interval—the period between trauma and the first appearance of symptoms, which averages from forty-eight to sixty hours, the briefest interval being thirty minutes and the longest nine days. Occasionally there is no free interval; this is particularly true in

instances of injury to the head. The second feature was rapid pulse, increased respiratory rate and elevation of temperature. These were so pronounced that the diagnosis of sunstroke was made, and treatment with cold packs was employed. Third, the cutaneous petechial hemorrhages that appeared on the third day were located chiefly over the abdomen, shoulders, extremities and conjunctivas. This sign has been emphasized by numerous authors, such as Fluornoy, Elting and Martin, Oppenheimer, Corlette, Fromberg, Hommerich, Weimann, Killian, Neubürger and Vance. Corlette asserted that this cutaneous sign was practically pathognomonic when taken in relation to all the other circumstances in the case. Cowling, in the clinical report of a case, made the diagnosis of cerebral fat embolism mainly on the basis of this change in the skin.

An interesting finding in our case was the ophthalmoscopic visualization of grayish, lusterless areas in the retina, which were difficult to explain at the time but may well have been embolic changes similar to those found in experimental animals after the induction of fat embolism. Several authors (Bernhard, Oppenheimer and Lillie) have detected the oval fat globules in the retinal vessels by means of the ophthalmoscope.

Vomiting, a symptom which is rare in cases of fat embolism, was present in our case throughout the clinical course. Elsner, who reported 3 cases in which there was hematemesis, observed fat emboli in the blood vessels of the wall of the stomach post mortem. Other confirmatory signs that have been described in cases of fat embolism are: (1) fat granules in the sputum (Elting and Martin), (2) fat globules in the urine and (3) fat in the blood and spinal fluid (Bürger). Roentgenographic examination of the chest has been suggested as a diagnostic aid in detecting pulmonary fat emboli (Scuderi).

The symptoms of cerebral fat embolism have been divided into three stages, which at times can be differentiated sharply but at others shade imperceptibly into one another: (*a*) period of the free interval previously mentioned; (*b*) the soporific stage, usually ushered in by dyspnea, precardial pains and increased pulse rate and followed by (*c*) the period of insomnia, amnesia, disorientation, delirium and stupor.

Without entering into a further discussion of the subject, we believe from the study of this case, as well as a survey of the literature, that investigation of the problem of cerebral fat embolism is indicated in the field of neurology. Such a study may help to shed additional light on (1) the bizarre neuropsychiatric syndromes, such as fractures and orthopedic manipulations, following trauma; (2) the unexpected fatal termination in cases of concussion of the brain from injuries to the head; (3) the unexpected, sudden appearance of mental symptoms and death following cranial and spinal operations; (4) the fatal outcome in some cases of status epilepticus, and, finally, (5) the bizarre cerebral reactions following such medical conditions as coronary thrombosis.

DISCUSSION

DR. HELENA RIGGS: I wish only to say that the brain is largely made up of fats. When the ganglion cells degenerate the fat breaks down. I do not see how one can determine whether fat is embolic or the result of degeneration. I have found the same picture in persons with heart disease who died in bed.

DR. MATTHEW MOORE: At present, my colleague and I have the brain of a man aged 54 who attempted suicide and, in so doing, fractured his hip. He was taken to the hospital, where he remained for several days, during which time he was apparently well. He suddenly became somnolent and rapidly sank into deep coma, in which condition he remained for approximately three days and then died. Dissection of the brain showed petechiae surrounded by small areas of necrosis distributed diffusely throughout the brain. We believe this to be a case of cerebral fat embolism secondary to fracture of the hip.

DR. J. C. YASKIN: This presentation has many important implications. There are interesting pathologic concepts and clinical findings, about which I am not altogether clear, and probably, most important of all, serious medicolegal aspects.

DR. ALFRED GORDON: Will the authors tell me whether the embolism in this case was localized in a particular part of the brain? Were the characteristic lesions more prominent in the basal ganglia than in any other part of the brain? The reason for asking this is that there was found first rigidity of the arms and subsequently flexion of the upper extremities.

DR. KENNETH M. CORRIN: The question arose in my mind about the possibility of fat emboli in a vein passing through the pulmonary circulation and thus reaching the brain. One would think that the pulmonary circulation would filter out the fat emboli. The lesions represented here resemble closely those that one sees in a cat or rabbit subjected over a period to severe convulsions.

DR. E. MARCOVITZ: In the cases that have been reported in the literature what was the usual latent period? What were the minimum and maximum latent periods and the intensity of cerebral symptoms? Can they be mild, or are they usually very severe? What was the usual outcome?

DR. J. C. YASKIN: My understanding is that an embolus is a foreign body which plugs a vessel. From this presentation I formed the concept that the patient showed emboli in the skin and in the renal apparatus. In other words, the blood stream was full of emboli—here, there and everywhere—which were eliminated through the urine. May I ask whether this is usual?

DR. ALEXANDER SILVERSTEIN: I am sorry that time did not permit the reading of the entire paper, since many of the questions would have been answered therein. In our case the clinical as well as the histopathologic picture was difficult to explain on the basis of an apparently minor injury to the lower extremities. Indeed, in the beginning the insurance company seriously questioned the direct relation of the trauma to the fatal outcome. That the trauma was directly responsible for the death of the patient was beyond question when all the factors were carefully considered. However, the mechanism responsible for the cerebral involvement and death was a mystery. It was only during a discussion of the case with Dr. Mona Spiegel-Adolph and Dr. Ernest Spiegel, one and one-half years later, that the diagnosis of cerebral fat embolism was suggested. They pointed out that a fracture of the extremity was not necessary to cause this complication. Dr. Ernest Spiegel not only suggested but verified the diagnosis by demonstrating with specific fat stains the typical fat emboli in the cerebral vessels. It must be confessed, however, that in spite of Dr. Spiegel's studies I was skeptical of the diagnosis of fat embolism and presented the slides to various persons for study. Dr. B. J. Alpers, who studied these slides, remarked that the case was the first of its kind that he had seen. It was only after reading several articles on fat embolism, especially that by Karl Neubürger, in the German literature, that it was believed that the case was one of typical cerebral fat embolism.

I suggest to those interested in the subject, particularly those who are skeptical concerning this syndrome, that they read a paper giving a comprehensive review (Groskloss, H. H.: *Yale J. Biol. & Med.* **8**:59 [Oct.] 1935. Vance, B. M.: The Significance of Fat Embolism, *Arch. Surg.* **23**:426 [Sept.] 1931. Strauss, H.: *Zentralbl. f. d. ges. Neurol. u. Psychiat.* **66**:385, 1933). I feel certain that they will be as surprised as I was to learn that cerebral fat embolism is a definite clinicopathologic syndrome which has been entirely overlooked by American neurologists.

As to Dr. Gordon's question relating to the decerebrate rigidity: In the beginning the attitude was that of extreme extension, both in the upper and in the lower extremity. Later, after two or three days, the posture changed to flexion in the upper limb and to extension in the lower, that is, the type of decerebrate rigidity usually described in man. The changes in the postural patterns of the rigidity in our patient resembled those found in acute and chronic preparations in animals. Microscopically, the most profound changes were seen in the basal ganglia and brain stem, the putamen being particularly involved.

Dr. Riggs stated that the fat emboli were due to degenerative changes in the cell. In the literature fat embolism is clearly differentiated from the fatty

degeneration that takes place in the cell. In our case globules of fat of various dimensions could be seen in the lumen of the vessels (as shown in the colored slides), often passing out of the capillaries. The oval fat globules in the vessels were entirely different from the fatty degenerative changes within the cell. Incidentally, we wish to make clear that none of the statements on cerebral fat embolism is based on any theory of our own—all the facts, including the pathologic observations, have been established by prominent authorities, such as Neubürger.

Dr. Yaskin asked how the emboli reach the skin and other parts of the body. It has been established that the fat liberated from trauma to fatty tissue is taken up by the veins and brought to the right side of the heart and then to the lungs. That a patent foramen ovale is not necessary for transmission of the fat from the right side of the heart to the systemic circulation has been proved by a number of investigators. From the lungs, the fat globules are forced through the pulmonary capillaries into the systemic circulation and carried to the brain, heart, kidneys, adrenal glands, skin and other structures. The involvement of the adrenal cortex may be one of the factors responsible for the shock reaction that may accompany fat embolism. Several authors have pointed out that systemic invasion of fat is more apt to occur in young, vigorous persons with strong myocardial musculature. Our case confirms this belief.

Dr. Marcovitz asked about the duration of the free interval. The usual periods vary between thirty-six to sixty hours—the briefest period being about thirty minutes and the longest, as reported, nine days. In cases of injury to the head, the coma from the injury may continue into the comatose stage of fat embolism, without a free interval.

MENINGOENCEPHALITIS DUE TO LYMPHOGRANULOMA VENEREUM. DR. HOWARD P. ROME (by invitation).

A brief review is made of the systemic nature of meningoencephalitis due to lymphogranuloma venereum and the paradoxic paucity of reports of its systemic distribution, particularly of localization in the central nervous system, in consideration of its prevalence, worldwide distribution and chronicity of infectivity.

REPORT OF A CASE

A Negress aged 25 had had anogenital manifestations for one year before the development of systemic lesions and those involving the central nervous system. The infection ran a protracted course (several months), characterized by intermittent elevation of temperature (from 101 to 105 F.), leukocytosis and hypochromic anemia. Neurologic examination revealed toxic delirium, with complete clouding of sensorium. There were nuchal rigidity, Kernig and Brudzinski signs, hyperreflexia, a transient Babinski sign and no demonstrable lesions of the cranial nerves. Examination of the spinal fluid revealed increased pressure, moderate pleocytosis and an increased protein content. The proteins of the blood were increased. The serologic reactions of the blood and spinal fluid and the colloidal gold reaction were negative. Cultures of the blood and spinal fluid, agglutination tests for typhoid, typhus, tularemia, undulant fever and paratyphoid gave repeatedly negative results. There was no rooentgenographic or bacteriologic evidence of tuberculosis.

The diagnosis was established by recovery of the virus from the spinal fluid and suppurating cervical nodes, with subsequent preparation of the Frei test with mouse brain and varied human antigens.

A positive reaction to the Frei test without clinical manifestation was present in the patient's 3 children (aged 4, 6 and 8 years) and in her consort.

Comment is made on 2 similar cases occurring in the same clinic, in which spontaneous remissions occurred and no sequelae were subsequently demonstrable.

DISCUSSION

DR. HELENA RIGGS: Within the last month I have had 2 patients, both from the psychopathic ward and both with acute mania. One, a girl, had terminal septicemia. The original infection was an open, gangrenous wound of the genital region. Later, she was admitted with acute mania. A positive blood culture was obtained, and she died within a short time.

DR. E. MARCOVITZ: I remember a case in the Neurological Institute of New York in which the difficulty of differentiating meningitis and tumor of the brain arose. In this case the diagnosis was made before the patient died.

DR. J. C. YASKIN: May I ask what one may expect of the laboratory in the way of a definite diagnosis? In other words, when one suspects such a condition what procedure shall one order to be carried out? Secondly, what, if any, treatment can be performed after the diagnosis is established? In the final analysis, these are two important facts to be borne in mind by those who practice clinical neurology.

In how many cases of this sort has autopsy been reported? In countries where this condition has been studied in greater detail, in what percentage of the cases of the disease is there involvement of the nervous system?

DR. HOWARD P. ROME: I do not know of any cases in which an autopsy has been reported. In approximately one third of the cases there is involvement of the nervous system. Prostigmine has been used in gradually ascending doses, without noteworthy effect.

Book Reviews

The Primate Thalamus. By A. Earl Walker. Price, $3. Pp. xxiii + 321, with 95 figures. Chicago: University of Chicago Press, 1938.

This excellent book presents the results of six years of research, conducted for the most part in the division of neurology and neurosurgery of the University of Chicago. The book deals with the thalamus of the rhesus monkey (Macaca mulatta), but enough work was done on the chimpanzee to show that the results hold also for this primate and are directly applicable to man. As a result of these years of investigation it has been possible for the author to present a classification of the thalamic nuclei based on the connections established by the ascending sensory pathways terminating in the thalamus and those established by the fibers running from the thalamus to the cortex. This classification does not differ greatly from those reached by Papez and Crouch on the basis of a histologic study of the normal thalamus.

The author recognizes within the thalamus: (1) an anterior nuclear group, consisting of the anteromedian, anterodorsal and anteroventral nuclei; (2) the nuclei of the midline, located in the walls of the third ventricle and in the massa intermedia; (3) the dorsomedial nucleus, formerly called the medial nucleus; (4) the intralaminar nuclei, situated within the internal medullary lamina and, so far as is known, receiving no ascending sensory fibers and sending no fibers to the cerebral cortex; (5) the nuclei of the medial and lateral geniculate bodies; (6) the pulvinar, and (7) the lateral nuclear mass, which was formerly called the lateral nucleus and which is subdivided into a dorsal and a ventral portion.

The dorsal portion of the lateral nuclear mass is designated as lateral and includes two parts, the nucleus lateralis dorsalis and the nucleus lateralis posterior. Neither of these nuclei receives ascending sensory fibers, and they are connected by thalamocortical fibers with the cortex of the parietal lobe behind the posterior central gyrus. The pulvinar receives no fibers from the optic tract or other sensory tracts, but does receive fibers from other thalamic nuclei and from the geniculate bodies. Fibers from the pulvinar run to the posterior part of the parietal and the temporal lobe. Like the nucleus lateralis dorsalis and nucleus lateralis posterior, the pulvinar serves for the integration of sensory impulses relayed to it from other thalamic nuclei.

The ventral portion of the lateral nuclear mass is larger than the dorsal and is subdivided into four parts: (1) The nucleus ventralis anterior forms the anterior end of the ventral part of the lateral nuclear mass. It receives no ascending sensory fibers and probably sends no fibers to the cerebral cortex. (2) The nucleus ventralis lateralis lies behind the preceding nucleus. It receives the termination of the fibers of the brachium conjunctivum and is connected by thalamocortical fibers with the motor cortex and, to a less extent, with the premotor cortex. Behind it are the posteromedial and posterolateral ventral nuclei. (3) The nucleus ventralis posteromedialis corresponds to what used to be called the nucleus arcuatus or semilunaris. It is molded on the medial surface of the centrum medianum, which is the largest of the intralaminar nuclei. It receives fibers from the secondary sensory trigeminal tracts and sends fibers to the face area of the sensory cortex. (4) The nucleus ventralis posterolateralis receives fibers from the medial lemniscus and spinothalamic tracts and sends fibers to the somesthetic sensory cortex. The secondary sensory fibers reaching the medial part of this nucleus carry afferent impulses from the arm, and those reaching the lateral part, impulses from the leg. The medial part projects to the arm area, and the lateral part to the leg area, of the cerebral cortex.

Dr. Walker's investigations have included a study of the histologic pattern of the thalamus, interruption of the various afferent tracts with a study of Marchi preparations showing the degenerated terminal fibers of these tracts and removal of areas of the cerebral cortex with a study of the retrograde cell degeneration in the thalamus to determine which nuclei of the thalamus send fibers to the ablated cortical areas.

A final chapter discusses in a fascinating manner the significance of the thalamus from physiologic and clinical points of view. The book has 95 good illustrations and a satisfactory index. It contains so much useful information that it should be read by every one seriously interested in neurology.

Correspondence

DISTRIBUTION OF AFFECTED NERVE CELLS IN A CASE OF AMYOTONIA CONGENITA

To the Editor:—In the article bearing this title, which appeared in the August 1938 issue of the Archives, pages 337-351, I stated that affected cells were seen in the globus pallidus. Further study of the sections has led me to the opinion that the affected cells ascribed to the globus pallidus and illustrated in figure 4 *C* are in the lateral part of the nucleus of the thalamus. These cells are large, oval and darkly stained and contain a large amount of Nissl substance. Whether they are efferent cells is not known.

No affected cells have been observed among the cells of the globus pallidus, which are elongated or multipolar.

J. LeRoy Conel, Boston.

CORRECTION

In the article by Drs. Carl F. List and Max Minor Peet, "Sweat Secretion in Man: II. Anatomic Distribution of Disturbances in Sweating Associated with Lesions of the Sympathetic Nervous System," which appeared in the July issue (Arch. Neurol. & Psychiat. **40**:27, 1938), in the references at the bottom of the first page there is a repetition of the line reading: "2d. The sympathetic connections with visceral organs are not considered here." The first line of the second reference should read: "2. (*a*) Guttmann, L., and List, C. F.: Zur Topik und Pathophysiologie der."